

Doctoral Programme in Population Health, University of Helsinki  
Public Health Promotion Unit, National Institute for Health and Welfare

# **DIET, DIABETES, AND PREVENTION OF COGNITIVE DECLINE**

**– FOCUS ON LIFESTYLE INTERVENTION**

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine  
of the University of Helsinki, for public examination in Auditorium XII,  
University Main Building, on 23<sup>rd</sup> of November 2018, at 12 noon.

Helsinki 2018

Cover illustration: Leena Turkka

Dissertationes Scholae Doctoralis Ad Sanitatem Investigandam Universitatis  
Helsinkiensis

ISBN 978-951-51-4620-5 (paperback)

ISBN 978-951-51-4621-2 (pdf)

ISSN 2342-3161 (print)

ISSN 2342-317X (online).

Unigrafia

Helsinki 2018

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# ABSTRACT

Late-life cognitive impairment and dementia are a burden for societies with ageing populations. In individuals with type 2 diabetes, the risk for dementia is elevated, and these disorders also share risk factors, such as obesity, as well as protective factors, such as healthy diet. It is possible to prevent type 2 diabetes with lifestyle changes, and thus, diabetes prevention could improve cognitive performance later in life. The influence of dietary factors on the development of dementia can be independent or through other risk factors, and a healthy diet may potentially prevent cognitive impairment through several pathways.

The main objectives of this study were to examine how midlife glycaemic control, diet, and physical activity predict subsequent cognitive performance within a diabetes prevention study and to elucidate the role of dietary guidance in older adulthood as a part of a multidomain lifestyle intervention aimed at preventing cognitive decline.

The study comprised data from two pioneering randomized, controlled lifestyle intervention trials. The Finnish Diabetes Prevention Study (DPS) included middle-aged participants at high risk for type 2 diabetes. Participants were invited to an ancillary cognition assessment at 8 and 10 years after the lifestyle guidance (n=364, mean age 68 years). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) included older adults at elevated risk for dementia (n=1260, mean age 69 years). A two-year multidomain lifestyle intervention was administered to prevent cognitive decline with dietary guidance, exercise, cognitive training, and management of cardiovascular risk factors. Cognitive performance was assessed with neuropsychological test batteries and participants completed food records in both studies.

In a population with impaired glucose tolerance, maintaining two-hour glucose response or HbA1c at normal levels in midlife predicted better visuomotor speed in later life, but incident diabetes over 13 years was unrelated to later cognitive performance. Long-term lower total fat and saturated fat intakes, body mass index, and waist circumference predicted better subsequent global cognitive performance. Weight reduction prior to cognitive assessment was associated with worse performance.

Among older adults, participation in a multidomain intervention resulted in improved diet quality measured with a dietary adherence score over two years. Intake of several vitamins and minerals decreased in the control group, but remained unchanged in the intervention group. Baseline dietary adherence score predicted improvement in global cognitive performance over two years, regardless of intervention allocation. Changes in dietary adherence score had a positive association with changes in executive

function, especially in the intervention group, but not with changes in other cognitive domains or global cognitive performance.

In conclusion, better midlife glycaemic control and healthier diet may protect from cognitive decline even among those who meet the criteria for impaired glucose tolerance, highlighting the importance of healthy lifestyle in high-risk groups. Worse cognitive performance among those who lost weight prior to cognition assessment could be explained by reverse causation, i.e. preclinical memory disorder may cause weight loss. Among older adults, targeted dietary counselling may prevent age-related decline in diet quality, thus preventing cognitive decline. For global cognition, baseline diet appeared more influential than dietary changes in two years, emphasizing the role of long-term healthy diet in supporting healthy brain ageing. Dietary changes in two years were nevertheless reflected in changes in executive function, indicating that cognitive benefits with dietary changes can be achieved in older age. These findings support the concept that diet has an important role in maintaining cognitive function in different phases of life.

# TIIVISTELMÄ

Muisti- ja tiedonkäsittelytoimintojen (kognitio) heikentyminen ja muistisairaudet muodostavat suuren haasteen väestön ikääntyessä. Muistisairauden todennäköisyys on suurempi niillä, jotka sairastavat tyypin 2 diabetesta. Myös monet taustatekijät ovat yhteisiä, esimerkiksi lihavuus lisää ja terveellinen ruokavalio puolestaan vähentää sairastumisen todennäköisyyttä. Tyypin 2 diabeteksen ehkäisy terveellisten elintapojen avulla on mahdollista, ja diabeteksen ehkäisy keski-ikässä saattaa parantaa myöhemmän iän kognitiivisia toimintoja. Ravintoaineet voivat vaikuttaa aivoihin sekä itsenäisesti että muiden riskitekijöiden kautta, joten terveellisen ruokavalion vaikutus kognition heikentymiseen voi välittyä useiden mekanismien välityksellä.

Tässä väitöskirjatutkimuksessa tutkittiin keski-ikänsä glukoosiaineenvaihdunnan ja elintapojen yhteyttä myöhemmän iän kognitioon diabeteksen ehkäisy tutkimuksessa, sekä tarkasteltiin ruokavalionmuutosten roolia kognition heikentymisen ehkäisyssä ikääntyneillä osana monimuotoista elintapaohjelmaa.

Tutkimuksen aineiston muodostivat kaksi suomalaista satunnaistettua elintapainterventiotutkimusta. Diabeteksen ehkäisy tutkimuksen (DPS) osallistujat olivat keski-ikäisiä ja heillä oli suuri todennäköisyys sairastua diabetekseen. Heidät kutsuttiin kognitiomittaukseen 8 ja 10 vuotta alkuperäisen elintapaneuvonnan jälkeen (n=364, keski-ikä 68 v.). Muistitoimintojen heikentymisen ehkäisy tutkimukseen (FINGER) kutsuttiin ikääntyneitä, joilla oli kohonnut todennäköisyys sairastua muistisairauteen (n=1260, keski-ikä 69 v.). Kaksivuotinen monimuotoinen kognitiivisen heikentymisen ehkäisyyn tähtäävä elintapainterventio sisälsi ruokavalioneuvontaa, liikuntaharjoittelua, kognitioharjoittelua sekä sydän- ja verisuonisairauksien riskitekijöiden tehostettua seurantaa. Psykologi toteutti laajan neuropsykologisen testistön vuosittain. Molemmissa tutkimuksissa tutkittavat täyttivät ruokapäiväkirjoja.

Tutkittavat, joiden glukoosiaineenvaihdunta pysyi normaalina DPS-tutkimuksen interventiojakson ajan, suoriutuivat paremmin visumotorista nopeutta mittaavassa testissä 8 vuotta myöhemmin, mutta diabeteksen kehittyminen 13 vuoden aikana ei ollut yhteydessä kognitioon. Matalampi rasvan ja erityisesti tyydyttyneen rasvan saanti koko 13 vuoden tarkastelujakson aikana ennusti parempaa kognitiota, kuten myös pienempi painoindeksi ja vyötärön ympärys. Kuitenkin painonlasku kognitiotutkimusta edeltävinä vuosina liittyi heikompaan suoriutumiseen.

Ikääntyneillä toteutetussa FINGER-tutkimuksessa Kaksivuotinen ruokavalioneuvonta paransi ruokavalion laatua interventoryhmässä. Monien vitamiinien ja kivennäisaineiden saanti laski vertailuryhmässä, mutta pysyi ennallaan interventoryhmässä. Ruokavalion parempi laatu lähtötilanteesta

ennusti kognition paranemista kahden vuoden aikana, riippumatta siitä kuuluiko tutkittava interventio- vai vertailuryhmään. Ruokavalion muutokset kahden vuoden aikana olivat erityisesti interventioryhmässä positiivisessa yhteydessä toiminnanohjauksen muutoksiin, mutta eivät muihin kognition osa-alueisiin.

Yhteenvetona voidaan todeta, että hyvä glukoosiaineenvaihdunnan säätely ja terveellinen ruokavalio keski-ikässä voivat suojata kognitiiviselta heikentymiseltä, vaikka heikentynyt glukoosinsieto olisi jo todettu. Terveellisten elintapojen ylläpitäminen on riskiryhmissä tärkeää myös kognition kannalta. Painonlaskun yhteys heikompaan kognitiiviseen suoriutumiseen voi selittyä alkavaan muistisairauteen liittyvällä painon putoamisella. Ikääntyneillä ravitsemussuosituksiin perustuva ruokavalioneuvonta on tehokasta ruokavalion laadun heikentymisen ehkäisyssä ja saattaa siten auttaa myös kognitiivisen heikentymisen ehkäisyssä. Kuitenkin alkutilanteen terveellinen ruokavalio vaikuttaa kognition muutokseen enemmän kuin ruokavalion muutokset kahden vuoden aikana, mikä korostaa pitkän aikavälin ruokavalintojen tärkeyttä aivoterveiden ylläpitämisessä. Ruokavaliomuutosten yhteys toiminnanohjauksen muutoksiin viittaa siihen, että myös korkeammassa iässä tehdyt muutokset voivat ehkäistä kognition heikentymistä. Nämä tulokset tukevat ajatusta siitä, että ruokavaliolla on tärkeä rooli kognitiivisten toimintojen ylläpitämisessä eri ikävaiheissa.

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# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I. Lehtisalo J, Lindström J, Ngandu T, Kivipelto M, Ahtiluoto S, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Eriksson JG, Uusitupa M, Tuomilehto J, Luchsinger JA. Finnish Diabetes Prevention Study Group. Diabetes, glycaemia, and cognition - a secondary analysis of the Finnish Diabetes Prevention Study. *Diabetes Metab Res Rev*. 2016;32(1):102-10.
- II. Lehtisalo J, Lindström J, Ngandu T, Kivipelto M, Ahtiluoto S, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Eriksson JG, Uusitupa M, Tuomilehto J, Luchsinger J. Finnish Diabetes Prevention Study Group. Association of Long-Term Dietary Fat Intake, Exercise, and Weight with Later Cognitive Function in the Finnish Diabetes Prevention Study. *J Nutr Health Aging*. 2016;20(2):146-54.
- III. Lehtisalo J, Ngandu T, Valve P, Antikainen R, Laatikainen T, Strandberg T, Soininen H, Tuomilehto J, Kivipelto M, Lindström J. Nutrient intake and dietary changes during a 2-year multi-domain lifestyle intervention among older adults: secondary analysis of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) randomised controlled trial. *Br J Nutr*. 2017;118(4):291-302.
- IV. Lehtisalo J, Levälahti E, Lindström J, Hänninen T, Paaanen T, Peltonen M, Antikainen R, Laatikainen T, Strandberg T, Soininen H, Tuomilehto J, Kivipelto M, Ngandu T. Dietary intervention adherence and cognition over 2 years within a multi-domain intervention trial – the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). *Alzheimers Dement* [in press].

The publications are referred to in the text by their Roman numerals and have been reprinted with the kind permission of their copyright holders. In addition, some unpublished material is presented.

# ABBREVIATIONS

AD	Alzheimer's Disease
A $\beta$	Amyloid beta
ApoE4	Apolipoprotein E $\epsilon$ 4 genotype
BMI	Body Mass Index
CA	Cognitive activity
CERAD	Consortium to establish a registry for Alzheimer's Disease neuropsychological test battery
CERAD-TS	Total composite score for the CERAD test battery
CT	Cognitive training
CVD	Cardiovascular disease
DASH	Dietary approaches to stop hypertension
DHA	Docosahexaenoic acid
DPS	Finnish Diabetes Prevention Study
EPA	Eicosapentaenoic acid
E%	Proportion of total energy intake
FA	Fatty acid
FFQ	Food frequency questionnaire
FINGER	Finnish Geriatric Intervention Study to Prevent Prevent Cognitive Impairment and Disability
HbA1c	Glycated haemoglobin
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
MCI	Mild Cognitive Impairment
MeDi	Mediterranean diet
MetS	Metabolic Syndrome
MIND	Mediterranean-DASH Diet Intervention for Neurodegenerative Delay
MMSE	Mini Mental State Exam
MUFA	Monounsaturated fatty acid
NTB	Neuropsychological test battery (as suggested by Harrison 2007)
OGTT	Oral glucose tolerance test
PA	Physical activity
PET	Positron emission tomography
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
SFA	Saturated fatty acid
TMT	Trail making test (in this thesis, refers to TMT-A with letters)
VaD	Vascular dementia

# 1 INTRODUCTION

Dementia is a neurodegenerative disorder with marked human, economic, and public health burden. The most common cause of dementia is Alzheimer's disease (AD), followed by cerebrovascular disease and their combination. Late-life dementia and cognitive impairment are sporadic, multifactorial, and develop slowly over time. More than 46 million people worldwide suffer from AD, and projections suggest that this figure will double every 20 years (Alzheimer's Disease International 2015), posing a growing challenge with ageing populations.

Risk for cognitive impairment increases gradually with age, and dementia was earlier considered an inevitable consequence of ageing. Within the last decades, numerous studies have been undertaken to study risk factors for dementia, and these studies have revealed associations between cardiovascular risk factors, e.g. obesity, hypertension, hypercholesterolaemia, and hyperglycaemia, and an increased risk of dementia.

Several factors that protect against the development of cognitive impairment have also been identified, many of which are shared by dementia and diabetes. Health-related lifestyles, such as good diet, physical exercise, and cognitive activity, as well as high education may protect against cognitive impairment. An estimated one-third of dementia cases are attributable to modifiable risk factors (Norton et al. 2014). No curative treatment is yet available, and thus, the focus of research has shifted towards preventive strategies, especially lifestyle interventions.

While observational evidence that relates overall healthy lifestyle with lower risk of cognitive impairment appears strong, trial data on possibilities to prevent dementia are still scarce. Understanding of the long preclinical period of AD has increased during the last decades, providing a window of opportunity for preventive actions. Meanwhile, this long period of non-symptomatic disease also poses questions about the right timing and population for preventive interventions, and may also confound associations in observational studies. The most effective strategy to prevent cognitive impairment would probably be a lifelong healthy lifestyle initiated already in childhood, however, such approaches are not feasible to test in clinical trials. Interventions conducted among healthy older adults at elevated risk for dementia could be most feasible for obtaining a measurable effect on cognitive performance in clinical trials.

Several small-scale short-term intervention studies designed to investigate prevention of cognitive decline were already initiated at the beginning of the 2000s, but the results were disappointing (Andrieu et al. 2015). Most early interventions probably targeted the disease too late, and the research focus has since shifted towards earlier stages of disease. In line

with this, the more recent trials are designed to detect subtle cognitive changes rather than conversion to dementia as their outcomes. Promising periods for prevention of cognitive impairment include midlife, at least partially through related risk factors, and earlier late adulthood when underlying preclinical memory disorders are not yet too advanced.

Changing only a single lifestyle factor may be insufficient to impact cognitive performance, and multidomain interventions have started to emerge in clinical trials. The Finnish FINGER study was among the first to show that lifestyle intervention was successful in affecting cognitive performance (Ngandu et al. 2015). While the multidomain approach is probably an optimal way to influence multifactorial conditions in clinical trials, the role of different components in the multidomain interventions should still be evaluated to optimize the content and quantity of future interventions.

In this study, lifestyle interventions, and especially dietary changes as a part of interventions, are examined in relation to cognition in cognitively intact populations at risk for diabetes or dementia. Lifestyle refers to health-related lifestyle factors such as diet, physical exercise, and mental activity. This literature review focuses on prospective studies and meta-analyses of prospective studies that investigate risk and protective factors for cognitive impairment among middle-aged or older participants, and that are considered relevant in the context of development of memory disorders. In this thesis, diabetes refers to type 2 diabetes, with type 1 diabetes being beyond the scope of this study.

## **2 REVIEW OF THE LITERATURE**

### **2.1 DEMENTIA, COGNITIVE IMPAIRMENT, AND COGNITIVE AGEING**

#### **2.1.1 DEMENTIA AND COGNITIVE IMPAIRMENT**

Dementia is the leading cause of disability among older adults, and its impact can be seen in individuals with dementia, their families and friends, and society. Dementia is both a human and economic burden. Current worldwide AD prevalence of 46 million is expected to increase to 131 million by 2050 (Alzheimer's Disease International 2015). In Europe, prevalence of dementia is estimated to be 4.7% among those >60 years. In Finland, at least 200 000 people have mild impairments in cognitive function, and almost as many have dementia, with estimates of 100 000 patients with mild dementia and 93 000 with moderate to severe dementia (Working group appointed by the Finnish Medical Society Duodecim et al. 2017).

In the Finnish Current Care Guidelines, the most common memory disorders are defined as AD, vascular cognitive impairment (earlier vascular dementia, VaD), Lewy body disease, Parkinson's dementia related to Parkinson's disease, and frontotemporal dementia (Working group appointed by the Finnish Medical Society Duodecim et al. 2017). AD is the main cause in approximately 70% and vascular cognitive impairment in 20% of the cases, and their combination is also common, especially among older patients. Vascular origins of cognitive impairment can be further divided into post-stroke dementia, subcortical ischaemic vascular dementia, multi-infarct dementia, and small-vessel disease (Skrobot et al. 2018).

The concept of mixed dementia was suggested after discovering that vascular pathologies co-occur with typical AD pathology among older patients (Langa et al. 2004), but its relevance has also been questioned because often "mixed" stands for comorbid disease that is not the primary cause of dementia (Dubois et al. 2007). Recent criteria suggest that specific combinations of AD-VaD or VaD-AD should be diagnosed rather than unspecific "mixed" type, depending on the dominating disease (Skrobot et al. 2018).

Clinical diagnosis of dementia is based on stepwise diagnostic criteria for AD (Jack et al. 2011, Dubois et al. 2014) and VaD (Roman et al. 1993, Perneczky et al. 2016), although there is an ongoing debate on diagnostic definitions. Diagnosis always requires a clinician to make a judgement, which is based on e.g. clinical features, biomarkers, and brain imaging. Clinical diagnoses have served as outcomes in several epidemiological studies, but recently research interest has shifted more to early detection of subtle changes in cognitive functions, especially in clinical trials, and

neuropsychological tests are increasingly used as an outcome. It has been suggested that clinical trials testing preventive strategies should not select dementia as an outcome since its incidence over a few years is low (clinical trials rarely last longer than 5 years), and thus, it is difficult to have a measurable effect (Andrieu et al. 2015). Furthermore, conducting preventive interventions just before the diagnosis of dementia may be too late to see any effects.

The underlying pathophysiological process of AD and its clinical symptoms (impairments in cognitive performance) are two related but distinct continuous trajectories that evolve in parallel, but they do not develop simultaneously or always progress at the same rate (Sperling et al. 2011). Separating these trajectories allows for definition of preclinical AD, which refers to the asymptomatic period, typically long, between the first pathological brain changes and manifest symptoms (Dubois et al. 2007), and prodromal AD, which refers to the symptomatic pre-dementia state characterized by some symptoms yet not severe enough to meet the diagnostic criteria for AD. So far, diagnosis of preclinical AD has been recommended only for use in research (Sperling et al. 2011).

Pathophysiological processes are ongoing for decades before the manifestation of symptoms, which has initiated the search for novel biomarkers to identify individuals at early stages of dementia. Currently, these biomarkers are better known for AD, where a decrease in amyloid beta ( $A\beta$ ) in cerebrospinal fluid (CSF) is considered the earliest detectable sign, followed by amyloid detected with positron emission tomography imaging (PET), CSF-tau and neurodegeneration measured by magnetic resonance imaging (MRI), and deficits in glucose metabolism detected by PET preceding the cognitive symptoms (Jack, Holtzman 2013).

Earlier, the transient phase between normal ageing and dementia has been identified with the concept of mild cognitive impairment (MCI), which is commonly defined as neither normal nor demented, with cognitive decline from the previous state and presence of subjective impairment, but preserved daily activities (Winblad et al. 2004). Cognitive impairment can affect a single domain or involve multiple cognitive domains, and specifically, the amnesic MCI (memory impairment) appears to be a risk factor for AD (Petersen et al. 2001). It has been suggested that diagnoses be developed towards diagnosing specifically early stages of AD or cerebrovascular disease rather than unspecific MCI (Dubois et al. 2007). Analogous to dementia, MCI research is undergoing a shift from investigating binary outcomes (conversion to dementia vs. no conversion) to continuous slopes in cognitive function (Dubois et al. 2007). Also, separate diagnostic criteria have been proposed for clinical work and research settings (Albert et al. 2011).

### **2.1.2 COGNITIVE PERFORMANCE AND COGNITIVE AGEING**

Cognitive functions are intellectual processes by which an individual becomes aware, perceives, and comprehends knowledge; they comprise aspects of perception, thinking, reasoning, and remembering. In epidemiological studies, cognitive functions are often categorized into processing speed, working memory (short-term), long-term memory, and acquired knowledge (Park, Reuter-Lorenz 2009). Executive functions are often viewed as one dimension of cognitive function, although they also differ from the neuropsychological perspective (Lezak et al. 2012).

Systematic age-related decline occurs in many domains of cognitive function already in midlife and thereafter (Alwin, Hofer 2008). Processing speed, working memory, and long-term memory decline with increasing age, while acquired knowledge remains stable (Park, Reuter-Lorenz 2009). Ability to exercise good sense and judgement is considered to improve with age (Alwin, Hofer 2008). Older individuals with normal cognition do not appear to forget more rapidly once they have learned something, but learning new things takes more time (Albert 1998). There is, however, always considerable variability, and intraindividual differences are greater among older participants than among the young (Park, Reuter-Lorenz 2009).

Identification of cognitive impairment and early diagnosis of dementia have undergone major improvements in the past decade, but it remains a challenge to differentiate the earliest pathological cognitive changes from the decline that can be viewed as “normal” ageing. Cognitive functions are assessed with various neuropsychological tests. Test performance is determined not only by capability in the specifically tested cognitive area, but also attention, verbal ability, and abilities to discriminate the stimuli of the test situation (Lezak et al. 2012). Many transient conditions, such as tiredness or depression, affect performance in tests, and older adults may be more susceptible to external confounding than younger people. Furthermore, education and other perceived properties have a major impact on the general level of cognitive function, and a single cross-sectional assessment may fail to differentiate a highly educated participant with a steep decline in performance from a less educated participant with stable cognitive performance.

Numerous tests evaluating different aspects of cognition are available, and they are often combined in a battery of tests. The most commonly used test batteries, such as the Mini Mental State Exam (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG), are widely used in clinical work and research, but they were developed to screen for AD and are not sensitive to more subtle cognitive changes, and hence, are not suitable for prevention studies among non-demented participants (Tsoi et al. 2015). In Finland, a Consortium to establish a registry for Alzheimers (CERAD) test battery (Morris et al. 1989) is often used to screen for dementia, but it also lacks sensitivity to detect subtle changes in participants without dementia. A novel scoring method, the CERAD total score, may



improve the test's sensitivity, at least in separating subjects with MCI from healthy participants (Chandler et al. 2005, Paajanen et al. 2010).

Test batteries with multiple tests are recommended for clinical trials because any single measurement will not capture impairment in different domains (Vellas et al. 2008). However, it remains unclear which tests are the most sensitive for very early AD or cognitive impairment due to cerebrovascular disease – failures in episodic memory are typically considered most relevant for AD (Dubois et al. 2014) and executive functions for VaD (Sudo et al. 2017) – but emerging evidence suggests that executive dysfunction may be identifiable in preclinical AD too (Mortamais et al. 2017). A neuropsychological test battery that combines several domains has been proposed as a valid alternative for research use (Harrison et al. 2007).

Furthermore, although neuropsychological tests are classified according to the primary cognitive domain believed to be necessary in completing the task, other cognitive skills are usually also needed, and thus, composite scores that measure global cognition have been recommended as outcomes for clinical trials (Harrison et al. 2007). This method has advantages, however, results depend on the specific tests chosen in the composite, and the order in which they are presented may also influence the results (Mortamais et al. 2017). There is a need to standardize the outcome measures, especially in clinical trials, as suggested in many recent reviews (Sperling et al. 2011, Andrieu et al. 2015, Downey et al. 2017).

### **2.1.3 NEUROPATHOLOGICAL CHARACTERISTICS OF DEMENTIA**

Mechanisms for cognitive impairment can be roughly divided into four main groups: local brain damage, metabolic disturbances, neuronal disturbances, and functional disturbances. Reasons for these disturbances can be further divided into curable; e.g. metabolic disturbances, such as B<sub>12</sub> vitamin deficiency or hypothyreosis, or functional disturbances, such as depression; permanent, e.g. after large infarcts or brain damage due to accident; or progressive, typically neuronal disturbances due to AD, cerebrovascular disease, or other types of dementia (e.g. Lewy bodies or frontotemporal dementia) (Winblad et al. 2016). Progressive mechanisms are those of interest in terms of prevention or slowing down the process of memory impairment as there is no cure available and they are becoming increasingly common in ageing populations.

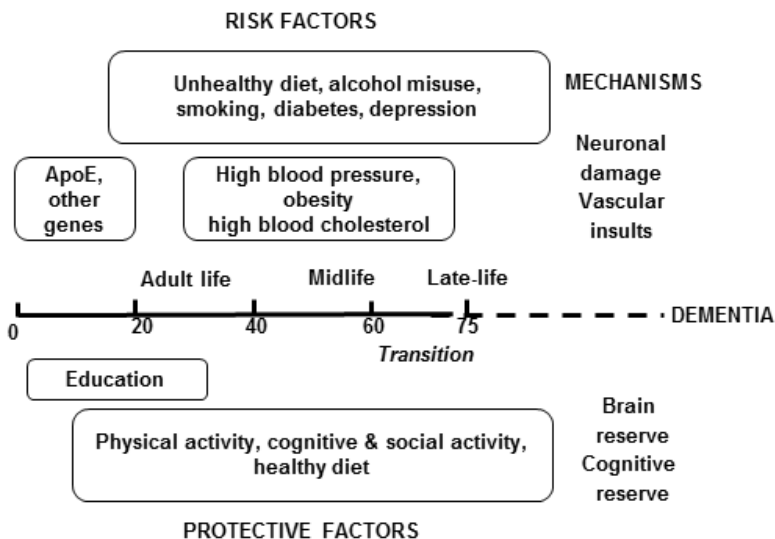
Pathological hallmarks of AD include the presence of A $\beta$  plaques, neurofibrillary tangles that contain hypophosphorylated protein tau, synaptic loss, neuronal loss, and degenerative changes in white matter (Raskin et al. 2015). The amyloid cascade hypothesis proposes that AD is caused by an imbalance between A $\beta$  production and clearance, resulting in accumulation of A $\beta$  in the brain as extra-neuronal plaques (Raskin et al. 2015). A $\beta$  deposition appears to be necessary, albeit not alone sufficient, for

development of AD, and probably synaptic dysfunction and neurodegeneration are needed to manifest symptoms (Sperling et al. 2011).

Dementia due to cerebrovascular disease is caused by reduced cerebral blood flow to the brain, which causes oxidative stress, hypoxia, and inflammation, which in turn affect mitochondrial function and neurovascular function (Raskin et al. 2015). This can be because of stroke, but does not have to be; the most common types of vascular cognitive impairment are small vessel disease, multi-infarct dementia (characterized by several small infarcts), and single infarct dementia. Vascular factors are also involved in A $\beta$  clearance, which is one mechanism linking the two main causes of dementia (Raskin et al. 2015).

## 2.2 RISK AND PROTECTIVE FACTORS FOR COGNITIVE DECLINE

Several risk and protective factors for cognitive decline have been identified (Figure 1). This section mostly focuses on modifiable risk factors of obesity, diabetes, and glycaemia. The most important non-modifiable risk factors, such as age and genes, and some other crucial modifiable risk factors, such as hypertension, are briefly overviewed.



**Figure 1.** Risk and protective factors for cognitive decline and dementia. Modified from Kivipelto et al. (2013).

### 2.2.1 NON-MODIFIABLE FACTORS

Age is the most important determinant of dementia risk: at 60-65 years of age, dementia prevalence is estimated to be below 2%, whereas after 90 years of age the prevalence varies between 33% and 63% (Prince et al. 2013). Young-onset dementia appears to have strong genetic component, with rare familial gene variants, whereas the late-onset type is sporadic, with differing aetiologies and influences from many modifiable risk and protective factors.

At least three gene variants are identified that almost inevitably lead to young-onset AD, but these cases account for less than 1% of the total disease (Karch, Goate 2015). Apolipoprotein E4 genotype (ApoE4; especially homozygotic E4/E4 allele) is the major genetic risk factor for sporadic AD. Recent genome-wide studies have identified more than 20 genetic loci that increase the risk of AD, but while these polymorphisms are frequent in the population, they contribute little to the risk for disease at an individual level (Karch, Goate 2015). Analogously, genetic susceptibility for VaD has been established for rare monogenic disorders, but less is known about the sporadic form, apart from the risk-increasing role of ApoE4. Genes identified in GWAS studies explain a low proportion of variance, and heritability of VaD remains largely unknown (Ikram et al. 2017). Some identified loci are associated with both AD and VaD (Sun et al. 2015).

Low education is considered the second most important risk factor for dementia, and a recent meta-analysis of 23 cohorts concluded that a 7% reduction in dementia risk would be attributable to a one-year increase in education (Xu et al. 2016). The linear relationship between education and cognitive function is well established (Meng, D'Arcy 2012, Beydoun et al. 2014), but results of studies investigating cognitive change over time are less consistent, with some showing a positive association (Schmand et al. 1997, Lyketsos et al. 1999, Alvarado et al. 2002) and others no association (Christensen et al. 2009, Wilson et al. 2009).

Education can be viewed as a modifiable factor, and has in fact been suggested to be among the most important modifiable risk factors (Beydoun et al. 2014). Modification of education at an individual level or in older age may, however, be difficult to achieve.

Education is likely to affect cognitive function through several pathways, one of which may be cognitive reserve. Hypotheses of the reserve were driven by observations that similar pathology does not always lead to similar clinical symptoms. The reserve can be divided into cognitive reserve, which refers to differences between individuals in compensatory approaches to brain changes, e.g. capability for greater neural network capacity, and brain reserve, which refers to differences in the brain structure that may help in tolerating the neuropathological changes, e.g. more neurons or synapses to lose (Stern 2012). Education and social activity are likely to play a role in cognitive reserve (Meng, D'Arcy 2012). A meta-analysis of 19 studies showed that low social participation, less frequent contacts, and loneliness increase

the risk of dementia (Kuiper et al. 2015), all suggested to play a role in cognitive reserve.

Socioeconomic status is an interplay between education level and occupational status and income, but based on a meta-analysis of 11 studies duration of education appears to be more important than occupational social class (Russ et al. 2013).

## **2.2.2 CARDIOVASCULAR RISK FACTORS**

Most conditions first recognized as risk factors for cardiovascular disease (CVD) have afterwards been shown to increase risk of dementia or cognitive impairment, e.g. hypertension, dyslipidaemia, obesity, and diabetes. Obesity may have a direct effect, but also indirect effects through contributing to other risk factors. Obesity, diabetes, and disturbances in glucose metabolism as risk factors for dementia are reviewed in the next sections.

A meta-analysis of 18 prospective studies found no overall association between blood pressure and incident dementia (Power et al. 2011), but age-stratification indicated a higher risk for AD with midlife hypertension and a lower risk with late-life hypertension. A deleterious effect of midlife elevated blood pressure was concluded in a meta-analysis focusing on midlife risk factors (Meng et al. 2014). Other meta-analyses have related elevated blood pressure with lower brain volume (Beauchet et al. 2013) and worse global cognition, episodic memory, and attention (Gifford et al. 2013). High blood pressure is a risk factor for stroke, which also increases risk of dementia (Zhou et al. 2015), and patients with MCI also have elevated risk for stroke (Rostamian et al. 2014). Furthermore, stroke risk at midlife is associated with accelerated cognitive decline (Kaffashian et al. 2013).

The significance of hypercholesterolaemia is more controversial, but two meta-analyses have concluded that high midlife total cholesterol increases risk of AD and any dementia (Anstey et al. 2008, Anstey et al. 2017), while late-life total cholesterol showed no association with any cognitive outcomes. AD may impact cholesterol homeostasis and confound causality in older age (Wood et al. 2014).

Metabolic syndrome (MetS) combines several risk factors and is characterized by abdominal obesity, elevated blood pressure, high blood glucose, elevated serum triglycerides, and low HDL cholesterol levels. A meta-analysis of longitudinal studies reported a small effect size, but significantly steeper cognitive decline among younger participants with MetS (<70 years) but not older participants (Siervo et al. 2014). After this meta-analysis, one study reported lower cognitive performance with MetS cross-sectionally, but similar cognitive decline over 6 years compared with healthy participants (Dearborn et al. 2014). In another 10-year follow-up, cognitive performance was lower among those with MetS, but cognitive change was not evaluated (Levin et al. 2014).

### 2.2.3 OBESITY, OVERWEIGHT, AND WEIGHT LOSS

The role of obesity in development of dementia is complex because preclinical AD causes weight loss and confounds the associations. Presence of the “obesity paradox”, beneficial overweight in later life, has been suggested for brain health (Monda et al. 2017) and is supported by a meta-analysis that showed increased risk of dementia with obesity before the age of 65 years and decreased risk with both overweight and obesity after the age of 65 years (Pedditizi et al. 2016). A more recent meta-analysis of 19 studies supports the detrimental effect of midlife obesity, i.e. Body Mass Index (BMI)  $>30 \text{ kg/m}^2$ , but not overweight ( $25 \text{ kg/m}^2 < \text{BMI} < 30 \text{ kg/m}^2$ ) for risk of dementia (Albanese et al. 2017). One meta-analysis suggested increased risk for AD with both midlife overweight and obesity, but increased risk for VaD only with overweight (Anstey et al. 2011). Furthermore, being underweight at midlife increases the risk of AD (Anstey et al. 2011, Albanese et al. 2017).

Studies that investigate overweight and cognitive function among non-demented older participants are scarce, but one study shows that being overweight or obese at midlife is associated with worse later cognitive function and more rapid decrease in cognition in older age (Dahl et al. 2013). Obesity or underweight measured at early adulthood, early midlife, and late midlife is also associated with lower executive function (Sabia S et al. 2009), as well as a large increase in BMI from early to late midlife. Obesity appears to decrease executive functions at all ages (Yang et al. 2018).

Weight change trajectories differ between those who develop dementia and those who do not; one study showed that from 28 to 12 years before the diagnosis BMI was higher, and thereafter, lower than same-aged controls, indicating rapid weight loss (Singh-Manoux et al. 2018). Although risk for AD is lower among those with higher late-life BMI, it does not appear protective in rapid weight loss (Bell et al. 2017). Intentional and unintentional weight losses are likely to have a divergent effect on cognitive function, yet their separation is challenging in epidemiological studies. A meta-analysis of intentional weight loss among cognitively healthy participants, predominantly middle-aged, concluded that attention, executive function, and memory were all improved after weight loss, but motor speed or language was not (Veronese et al. 2017). These studies were referred to as observational, but they all included an intervention of some type, e.g. observational studies after bariatric surgery, or pilot lifestyle intervention trials without a control group. Except for one study, participants were  $<60$  years of age on average, and generalizability of the results in older adults or contribution of these cognitive changes to dementia risk is unclear.

#### **2.2.4 DIABETES**

After discovering that brain insulin intolerance and insulin deficiency are among the metabolic characteristics of AD in animal models, some authors have suggested that AD is a neuroendocrine disorder and should be referred to as “type 3 diabetes” (Steen et al. 2005, Pilcher 2006). Several molecular pathways have been identified to explain the association between diabetes and AD (Mittal et al. 2016). While decrements in brain glucose metabolism already in early AD are well recognized, the significance of “type 3 diabetes” still a matter of debate. The ageing brain could become more susceptible to cellular damage induced by high levels of circulating glucose, which would then explain cognitive changes observed in patients with diabetes (Gonzalez-Reyes et al. 2016).

Meta-analyses show constantly that diabetes increases the risk for both AD and VaD. The most recent study reported a 60% increase in risk of any dementia among individuals with diabetes (Chatterjee et al. 2016). Risk ratios for non-vascular dementia were similar for both sexes, but the risk for VaD was greater among diabetic women. Estimated risk ratios were slightly lower than those presented previously (Cheng et al. 2012, Gudala et al. 2013). Diabetes also increases risk for MCI (Cheng et al. 2012).

Despite epidemiological evidence linking diabetes to both VaD and AD, neuropathological studies have reported similar AD pathology with diabetes and without (Thambisetty et al. 2013, Abner et al. 2016) or even less AD pathology with diabetes (Ahtiluoto et al. 2010), but more vascular pathology (Ahtiluoto et al. 2010, Thambisetty et al. 2013). The authors speculated that less AD pathology may be needed to manifest dementia in diabetes.

Studies show relatively consistently some decrements in cognitive performance also among non-demented participants with diabetes relative to those without, at all ages. A recent meta-analysis reported that individuals with diabetes had lower episodic memory, logical memory, phonemic fluency, cognitive flexibility, and speed of processing, but similar short-term and working memory compared with non-diabetic participants (Sadanand et al. 2016). Two previous meta-analyses concluded worse performance with diabetes in all studied domains, but effect sizes between domains varied, with attention suggested as having the smallest (Palta et al. 2014) or largest effect (Monette et al. 2014), and all effect sizes were small to moderate. Cross-sectional studies were included in all of these analyses together with longitudinal studies. According to a meta-analysis, neither duration of diabetes nor BMI moderated the association between diabetes and cognition, but higher HbA1c level was associated with more severe deficits (Mansur et al. 2018).

Worse cognitive performance in diabetes is quite consistent in studies with a single cognitive assessment either cross-sectionally or prospectively after evaluation of baseline diabetes status. Findings on cognitive decline over time in diabetes are less consistent. Within periods of 4 to 6 years, some studies suggest steeper diabetes-related decline (Kanaya et al. 2004, Palta et

al. 2017), while no difference compared with healthy participants has also often been reported (van den Berg et al. 2010, Kohler et al. 2012, Bangen et al. 2015). In 12 years, an accelerated decline with prevalent diabetes was evident in a study showing no differences after 6 years (Spauwen et al. 2013). A long latency period is supported by other studies reporting a greater cognitive decline among those with prevalent diabetes in 14-year (Knopman et al. 2009) and 20-year follow-ups (Rawlings et al. 2014).

### **2.2.5 GLYCAEMIA**

Analysing glycaemia provides more insight into the association between diabetes and cognitive performance, which is confounded by, for instance, the method used to define diabetes and the duration, severity, and control of diabetes. A systematic review concluded that in diabetes HbA1c concentration and glucose variability are negatively associated with cognitive function, but not with the risk of dementia (Geijselaers et al. 2015). Previously measured higher HbA1c predicted accelerated cognitive decline in a population with diabetes (Feinkohl et al. 2015), and a cross-sectional interaction between diabetes duration and HbA1c suggested that diabetes duration affects cognition, especially with high HbA1c, i.e. when diabetes is not well controlled (West et al. 2014). The difference in decline between poorly and well-controlled diabetes at midlife was also evident in the 20-year cognitive change (Rawlings et al. 2014). One study suggested that those with elevated HbA1c but no diabetes diagnosis have higher risk of dementia than those with well-controlled diabetes (Ramirez et al. 2015).

In addition to hyperglycaemia, also hypoglycaemia increases the risk of dementia among older adults treated with glucose-lowering medication (Mattishent, Loke 2016). This relationship appears two-sided though, i.e. dementia also increases the risk of hypoglycaemia. Medications need to be considered carefully, especially among older adults (Scherthaner, Scherthaner-Reiter 2018). One study has shown that decreasing glucose levels precede dementia (Hendrie et al. 2018), but this was evident only among African-American participants, not Caucasians.

Blood glucose levels are a continuum beyond the cut-offs for diabetes, and fasting glucose, response to OGTT, or HbA1c levels may have effects on cognitive function at any levels. Two studies have suggested that higher fasting glucose may be associated with elevated risk of dementia already among those with glucose values within the normal range (Mortimer et al. 2010, Crane et al. 2013). In 15 years of follow-up, IFG was not associated with dementia, but IGT increased the risk of any dementia and AD (Ohara et al. 2011). Risk of VaD was not elevated in that study, while a previous study reported increased risk of specifically VaD (Curb et al. 1999).

Evidence for glucose levels and cognitive decline over time are scarce. Midlife prediabetes (defined based on HbA1c) has been associated with greater cognitive decline in 20 years, similar to the effect of prevalent

diabetes (Rawlings et al. 2014). Higher fasting glucose was related to greater decline in general cognitive ability and several cognitive domains over 16 years in a mixed population with and without diabetes (Seetharaman et al. 2015), but not over 4 years (Euser et al. 2010). Over 2 years, incident diabetes or IFG were associated with more cognitive decline, but prevalent stable IFG was not (Samaras et al. 2014). One study suggested that an increase in HbA1c was associated with cognitive decline in a non-diabetic population (Ravona-Springer et al. 2012).

To summarize, evidence is scattered and suggestive of impaired glucose metabolism predicting impaired cognitive function, but insufficient for any conclusions to be drawn about the relative importance of different glucose measures or specific time windows when glycaemia control would be the most crucial. An overview of the studies related to diabetes, glycaemia, and cognitive performance is presented in Table 1.

## **2.2.6 OTHER MODIFIABLE FACTORS**

Together with diet, physical activity (PA) and cognitive and social activity (CA) are most often proposed as lifestyle features that may help in maintaining cognitive abilities.

A recent meta-analysis of 32 cohorts with at least a one-year follow-up showed that higher PA predicts lower risk of all-cause dementia, AD, and cognitive decline, but it is not associated with VaD (Guure et al. 2017). Similarly, a meta-analysis focusing on leisure-time PA found a dose-response inverse trend for risk of all-cause dementia and AD, but not for VaD (Xu et al. 2017). Previously, higher PA has been associated with reduced risk of cognitive decline and dementia in all adults >40 years (Blondell et al. 2014), and reduced risk of AD also when PA was evaluated after 65 years of age (Beckett et al. 2015). Risk of cognitive decline may be reduced already with low-to-moderate exercise relative to no exercise (Sofi et al. 2011).

At least one systematic review has summarized that late-life CA is protective of AD and any dementia (Sajeev et al. 2016), and another concluded that social relationships have an association with cognitive function (Kelly et al. 2017).

In addition to PA and CA, other modifiable factors that have fairly consistently shown a risk-increasing relationship with dementia include depression, smoking, and high homocysteine levels (Beydoun et al. 2014, Zhong et al. 2015, Bellou et al. 2017).



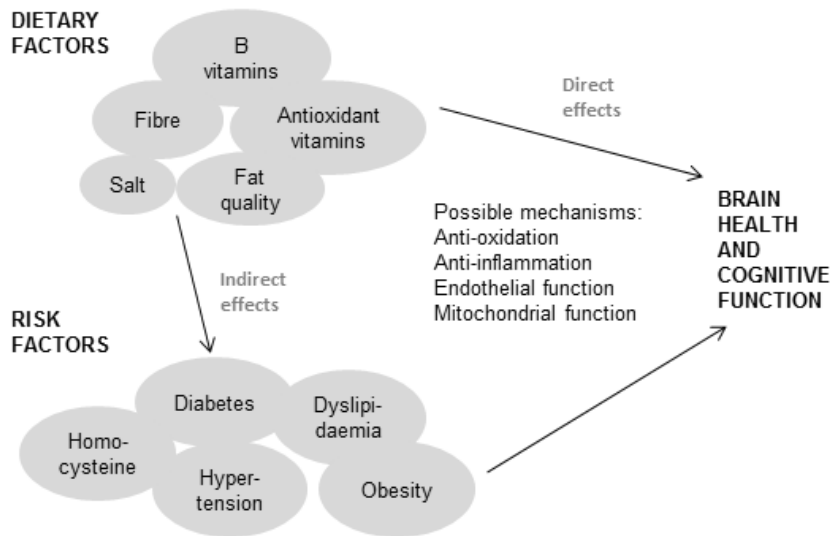
**Table 1.** Overview of studies investigating diabetes or glycaemia in relation to cognitive performance or dementia.

Observational studies			Trial evidence	
	Risk of dementia	Risk of MCI	Cognitive performance in cross-sectional setting	Cognitive decline in longitudinal setting
<b>Diabetes (vs. no diabetes)</b>	Several meta-analyses ↑	One meta-analysis ↑	Several meta-analyses ↑	Inconsistent findings within few years (↑↔) More consistent with follow-ups >10 years ↑
<b>Prediabetes (vs. normoglycaemic)</b>	Few prospective studies using IGT or HbA1c (↑) Few prospective studies using IFG ↔	Few prospective studies using IFG (↔)	Few studies using IFG (↔)	Two diabetes prevention trials in populations with prediabetes ↔ (secondary analyses)
<b>Fasting glucose concentration</b>	One systematic review (in diabetes) ↔ Few prospective studies in non-diabetic populations (↑)	n/a	One study in non-diabetic population ↑	Few prospective studies in non-diabetic population ↑
<b>HbA1c concentration</b>	One systematic review (in diabetes) ↔ Few prospective studies study in non-diabetic populations (↑)	One systematic review (in diabetes) ↔	One systematic review (in diabetes) ↑ One prospective study in non-diabetic population (↑)	One systematic review (in diabetes) ↔ Few prospective studies study in non-diabetic populations (↑)

↓ associations with decreased risk or better performance ↑ associations with increased risk or worse performance ↔ no association. Parentheses indicate that evidence is inconclusive. n/a, data not available.

## 2.3 DIET IN DEVELOPMENT OF COGNITIVE DECLINE

Mechanistic and animal studies have identified a wide variety of pathways that link dietary factors to neuropathological processes involved in the development of dementia, e.g. increased oxidative stress, defects in mitochondrial function and cellular energy production, chronic inflammatory mechanisms, and even direct pathways to A $\beta$  accumulation and neurofibrillary degeneration (Swaminathan, Jicha 2014). Furthermore, dietary factors have well-established associations with the CVD risk factors that were reviewed in the last section, and thus, the association between diet and neurodegeneration may at least partly be mediated through other risk factors like cholesterol and blood pressure (Morris 2012). An overview of the role of dietary factors for brain health is presented in Figure 2.



**Figure 2.** Direct and indirect effects of dietary factors on brain health and cognitive function.

### **2.3.1 DIETARY ISSUES AMONG OLDER ADULTS**

Both midlife and long-term diets probably have important roles in development of later cognitive impairment, but in terms of dementia prevention trials, older adults are usually chosen as the target group. Among older adults, issues related to dietary changes in ageing should be considered when planning a lifestyle intervention.

With increasing age, people undergo physiological changes, including reductions in muscle mass and bone density and decreased immune function. These changes together with decreased absorption of some nutrients and reduced total energy intake may make it harder to meet nutrition requirements in older people (Bernstein et al. 2012). Energy expenditure and metabolic rate decrease with ageing, contributing to decreased energy intake (Roberts, Dallal 2005). Quality of diet may become even more important when energy intake declines because micronutrient requirements do not appear to decline proportionally (Bales et al. 2015). Higher protein intake and higher BMI are generally recommended for older adults, but limited research has evaluated the suitability of general dietary recommendations for independently living older adults. Older adults are a heterogeneous group, often with morbidities, and simply based on chronological age their dietary requirements may vary more than among younger people. Food intake decreases with ageing, which has been associated with lower intakes of, for example, B-vitamins, vitamin E, and zinc (Drewnowski, Shultz 2001). The contribution of dinner to the total energy intake was shown to decrease, and breakfast and snacks to increase, especially among men (Vincent et al. 1998), which led to lower lipid and higher carbohydrate intake.

In Finland, dietary recommendations specifically for older adults have been launched (National Nutrition Council 2010), but nutrient intake recommendations are based on those for the whole population. For home-dwelling relatively healthy older adults, the guidelines are very similar to those for the general population, other than emphasizing adequate energy intake and protein intake of 1-1.2 g per kg body weight. The general recommendations (National Nutrition Council 2005) have been updated (National Nutrition Council 2014), and the recent version introduces a higher requirement for adequate protein among older adults (15-20% of total energy intake, E%) and advises the use of supplemental vitamin D year round.

While dietary guidelines can be important in health promotion, they are often focused on reducing the risk of chronic diseases or preventing nutrient deficiencies, and their suitability for promotion of healthy ageing is uncertain (Mathers 2013), and even more so for promotion of healthy brain ageing.

Although detrimental changes in diet with ageing could be a target for dietary interventions, evidence related to interventions among home-dwelling older adults is limited. A meta-analysis investigating feasibility and effectiveness of dietary intervention trials in retirement age identified 22 trials within the age range of 54-70 years (Lara et al. 2014), however, in most

studies the mean age was <60 years and participants could be considered middle-aged. These trials most often promoted a Mediterranean diet (MeDi) or increased fruit and vegetable intake, followed by other healthy diets such as decreased fat intake or modified fat quality, mostly for overweight or obese participants. The trials were concluded to be effective in terms of increasing fruit and vegetable intake and promoting fish consumption while diminishing red meat consumption.

A more recent umbrella review identified 25 systematic reviews and 3 meta-analyses covering all types of nutritional trials among those >65 years, including supplement trials, that examined either improvements in nutritional indices or any outcomes related to healthy ageing (Poscia et al. 2017). Due to the heterogeneous nature of both interventions and outcomes, no firm conclusions were drawn except from the effect of vitamin D supplementation on prevention of falls. Several types of intervention, either environmental modifications or education, were shown to be effective in terms of improving energy intake or protein intake or reducing the risk for malnutrition.

In Finland, dietary intervention has been applied as a part of multidomain intervention together with exercise to prevent cardiovascular disease (Komulainen et al. 2010). Also, among patients with AD and their spouses a small-scale intervention has shown that diet can be improved by an intervention (Suominen et al. 2015).

Most previous nutritional interventions have been targeted to “young-older” adults aiming at reduction of weight and cardiovascular risk factors; or to frail or disabled older adults aiming at increased energy intake and securing adequate dietary intake. Transient phase between these groups is less studied. The retirement period could be a window of opportunity for lifestyle improvements and interventions (Lara et al. 2014).

### 2.3.2 INTRODUCTION TO DIETARY PATTERNS

Together with challenges in estimating typical food intake, the definition of a healthy diet remains a methodological challenge. The diet of an individual contains both healthy and unhealthy properties, and there is an interplay between healthy foods in unhealthy amounts and vice versa. Furthermore, combinations of foods and nutrients may have synergistic effects (Alles et al. 2012). The dietary pattern method, where an overall measure of dietary quality is calculated, is popular when data for the whole diet are available. These approaches can be divided into *a posteriori* methods, where statistical analysis methods are used to extract the dietary patterns within the specific population, and *a priori* methods, i.e. dietary indices, where pre-specified components are scored (Hu 2002). Of the two approaches, *a priori* methods are more commonly used, and a combination of the two, reduced rank regression, has been suggested as a novel method (Tucker 2010).

Numerous dietary patterns or dietary indices have been proposed, but the MeDi, originally introduced in 1995 (Trichopoulou et al. 1995), is the most extensively studied. It is characterized by high intake of vegetables, fruits, legumes, whole grain, fish, and olive oil and low intake of meat and dairy. Other commonly used indices include dietary approaches to stop hypertension (DASH) (Fung et al. 2008), originally developed to decrease hypertension and characterized by low sodium intake and high intake of fruits, vegetables, and whole grain, and recommendation-based indices such as the US Healthy eating index (HEI) (Kennedy et al. 1995), with its modified (AHEI) (McCullough et al. 2002) and updated versions (HEI-2010) (Guenther et al. 2013). Other indicators estimating adherence to dietary recommendations have been introduced in Finland and in Sweden (Drake et al. 2011, Kanerva et al. 2013a) and to WHO guidelines for the prevention of chronic diseases (HDI) (Huijbregts et al. 1998). Also a Nordic healthy diet index has been introduced (Kanerva et al. 2013b, Hillesund et al. 2014). One index has been proposed specifically for older adults (Kourlaba et al. 2009), and one for measuring inflammatory properties of the diet (Shivappa et al. 2014).

*A priori* indices can be further divided into those based on pre-specified cut-offs, typically indices estimating adherence to recommendations, and sample-driven cut-offs such as median or quartiles. For MeDi and DASH, both scoring methods have been applied.

### **2.3.3 DIETARY PATTERNS AND COGNITIVE PERFORMANCE**

The most extensively studied dietary index in relation to cognitive function, and virtually all other health outcomes, is the MeDi. Studies reporting an association of the MeDi with AD and cognitive impairment started to emerge more than a decade ago (Scarmeas et al. 2006, Fearnt et al. 2009, Scarmeas et al. 2009), and a vast number of studies have since been published, followed by reports of other dietary patterns such as the DASH and the various versions of the HEI (Table 2).

A recent systematic review identified 13 previous systematic reviews of the MeDi and cognitive function or risk of dementia in observational studies (Radd-Vagenas et al. 2018). The most recent of these included only cohorts with follow-up >5 years and concluded that high adherence to the MeDi is associated with a lower risk of cognitive disorders than low adherence, but modest adherence is not associated with lower risk (Wu, Sun 2017). These associations were seen for MCI and AD, but not any dementia, concordant with an earlier analysis (Singh et al. 2014). Among cognitively intact participants, a meta-analysis of 15 cohorts concluded that adherence to MeDi is associated with episodic memory and global cognition, but not working memory or semantic memory (Loughrey et al. 2017).

A meta-analysis that combined DASH, HEI, and AHEI observed an overall association between dietary patterns and neurodegenerative diseases,

however, this analysis included also Parkinson's disease together with AD and MCI (Schwingshackl et al. 2018). Adherence to the DASH has predicted less cognitive decline or lower risk of AD among older adults in at least three prospective studies (Wengreen et al. 2013, Morris et al. 2015b, Berendsen et al. 2017b), but not in all studies (Haring et al. 2016). Two prospective studies have evaluated the association between HEI or AHEI and cognitive function, with inconsistent results (Tangney et al. 2011, Smyth et al. 2015, Haring et al. 2016), and HDI was not associated with cognition in two studies (Olsson et al. 2015, Berendsen et al. 2017a). More recently, an inverse association between dietary inflammatory index and cognitive decline has been demonstrated in many cohorts (Hayden et al. 2017b, Kesse-Guyot et al. 2017, Frith et al. 2018). The Healthy Nordic diet predicted better cognitive performance in one Finnish prospective study (Männikko et al. 2015), although the associations were not significant after adjustment for total energy intake.

After discovery of associations between established dietary indices and cognitive function, the first brain-healthy dietary pattern has been introduced. The Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) (Morris et al. 2015a) combines properties of the MeDi and DASH and modifies them with findings in the diet-dementia field. Another important property of MIND is pre-specified cut-offs instead of population-based scoring, which the developers considered important to improve comparability between studies (Morris 2016). Higher adherence to MIND has been associated with slower prospective global cognitive decline (Morris et al. 2015a), better verbal memory (Berendsen et al. 2018), and lower risk of AD (Morris et al. 2015b) in prospective studies, and cross-sectionally with better cognitive function and less cognitive impairment (McEvoy et al. 2017).

#### **2.3.4 VEGETABLE, FRUIT, AND FISH CONSUMPTION**

Studies of single foods and nutrients in relation to cognitive function are abundant, but many of them are cross-sectional, performed in an age group not relevant here, or with poor methodology. There are also many studies of good quality, and this section is restricted to dietary approaches with targeted substudies, i.e. DPS and FINGER main intervention goals, hence focusing on macronutrient intake and consumption of fruits, vegetables, and fish.

**Table 2.** Most common dietary indices studied in relation to dementia or cognitive function.

Dietary index	Components	Risk of dementia	Cognitive performance <sup>e</sup>	Cognitive decline <sup>1</sup>	Trial evidence
<b>Mediterranean Diet</b> (Trichopoulou et al. 1995; has been since modified)	Vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, ethanol, monounsaturated:saturated fat ratio; scoring based on sex-specific median, range 0-8.	Several meta-analyses ↓	Several meta-analyses ↓	Several meta-analyses ↓	One meta-analysis (↓)
<b>DASH</b> (Fung et al. 2008, modified several times)	Fruits, vegetables, nuts and legumes, low-fat dairy products, whole grains, sodium, sweetened beverages, red and processed meats; scoring based on sex-specific quintiles, range 8-40.	Several prospective studies ↓	Several prospective studies ↓	Several prospective studies ↓	One 6-month trial ↓
<b>MIND</b> (Morris et al. 2015)	Green leafy vegetables, other vegetables, berries, nuts, olive oil, butter or margarine, cheese, whole grains, fish (not fried), beans, poultry (not fried), red meat and products, fast fried foods, pastries and sweets, wine; pre-specified cut-offs, range 0-15.	One prospective study ↓	One prospective study ↓	Two prospective studies ↓	n/a
<b>HEI or AHEI</b> (Kennedy et al. 1995, modified versions Guenther et al. 2013; or McCullough et al. 2002 )	Original HEI: grains, vegetables, fruits, milk, meat, total fat, saturated fat, cholesterol, sodium, variety; pre-specified cut-offs; range 0-100; modified versions include intake of beans, legumes; separation of whole grain and refined grain, and empty calories; AHEI: vegetables, fruit, nuts and soy protein, white: red meat ratio, cereal fiber, trans-FA, PUFA:SFA ratio, duration of multivitamin use, alcohol; range 2.5-87.5.	One prospective study ↔	Two cross-sectional studies ↓	Three prospective studies (↓)	n/a

↓ associations with decreased risk or better performance ↑ associations with increased risk or worse performance ↔ no association. Parentheses indicate that evidence is inconclusive. <sup>1</sup> Definitions vary over studies; meeting status of mild cognitive impairment or decline from previous performance.

Three meta-analyses have recently concluded that higher consumption of fruits and vegetables is associated with lower risk of cognitive impairment and dementia combined (Jiang et al. 2017); any type of cognitive disorders (Wu et al. 2017), and MCI (Mottaghi et al. 2017). After these meta-analyses, at least one additional study has supported the findings (Lee et al. 2017). Less is known about the effects of vegetables and fruits on cognitive function among non-demented participants. One study suggested beneficial effects over 3 years (Chen et al. 2012), whereas two others show inconsistent results (Nooyens et al. 2011, Peneau et al. 2011). An earlier meta-analysis has shown benefits of fruit and vegetable consumption on risk of stroke (He et al. 2006), which suggests benefits also on cognitive performance.

An association between higher fish consumption and lower risk of any dementia was described in a recent meta-analysis (Bakre et al. 2018), supported by a previous analysis that also reported lower risk of AD and any dementia, but not of MCI (Zhang et al. 2016). One meta-analysis suggested lower risk of AD, but not any dementia (Wu et al. 2015). Data on cognitive function among non-demented older adults are modest, but a beneficial effect of fish consumption has also been shown in cross-sectional (Nurk et al. 2007, Danthiir et al. 2014) and longitudinal studies (van Gelder BM et al. 2007, van de Rest et al. 2009, van de Rest et al. 2016). A recent meta-analysis of five unpublished cohorts reported an association between increased fish consumption and less memory decline among healthy participants (Samieri et al. 2018). One study suggested that benefits are only evident among those aged over 65 years (Qin et al. 2014).

### **2.3.5 MACRONUTRIENT INTAKE**

Data on energy-yielding nutrients in relation to cognitive performance are limited, but the role of dietary fats has been studied the most extensively. Especially the intake of marine-derived fatty acids, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been a subject of interest, but research has been more focused on supplemental use. One recent meta-analysis suggested that dietary intake of DHA is associated with lower risk of AD (Zhang et al. 2016), but without a dose response, whereas another found no association (Wu et al. 2015).

Intake of saturated fatty acid (SFA) and trans fatty acid has been evaluated in one systematic review, which reported an association between SFA intake and risk of AD in most of the studies, but inconsistent results related to SFA and any dementia or MCI (Barnard et al. 2014). Studies on trans fatty acid intake were sparse and showed mixed results. Among non-demented persons, higher intake of saturated fat may be associated with more cognitive decline (Morris et al. 2004, Okereke et al. 2012), but findings are inconsistent (Vercambre et al. 2010, Naqvi et al. 2011).



The role of carbohydrate quality is very poorly known, and total carbohydrate intake was analysed in one study, which showed an association between higher intake and higher risk of MCI in a 3-year follow-up (Roberts et al. 2012). A few studies have suggested a beneficial effect of dietary fibre on cognitive decline (Vercambre et al. 2009) or cross-sectional cognitive performance (Ortega et al. 1997), and whole-grain intake (Wengreen et al. 2013) or non-refined cereal (Anastasiou et al. 2017) have been reported to protect against cognitive decline. Prospective studies of sugar or sucrose intake in relation to cognitive function are lacking, but one prospective study suggested that artificially sweetened drinks increase the risk of dementia, while sugary drinks showed no such association (Pase et al. 2017). Sugar intake had an inverse association with cognition in a cross-sectional study (Taylor et al. 2017), which also described an association of both sugar and total carbohydrates with brain A $\beta$  burden.

Due to disturbances in brain glucose metabolism among persons with dementia, a ketogenic diet with a very low proportion of energy from carbohydrates has been suggested as a potential treatment (Cunnane et al. 2016), but collecting epidemiological data on a ketogenic diet is challenging and no studies have reported its association with cognition.

Dietary protein intake in relation to cognitive function has also been rarely studied. A systematic review identified five cohort studies, of which three showed no association and one a protective association of higher protein intake in terms of cognitive function and risk of MCI (Koh et al. 2015). Also cross-sectional studies have shown inconsistent results, but in case-control studies people with dementia had lower intakes of protein (van de Rest et al. 2013).

Alcohol consumption has been a topic of interest, but less studied in recent years. A meta-analysis from 2009 concluded that moderate drinkers had a lower risk of AD, VaD, and any dementia than non-drinkers, and a lower risk of AD and any dementia was also present among all drinkers than among non-drinkers (Anstey et al. 2009). A previous meta-analysis in 2008 showed that small amounts of alcohol may reduce the risk of AD and any dementia, but not VaD or cognitive impairment (Peters et al. 2008). Better cognitive function among those with moderate alcohol consumption has been reported in many studies (Zanjani et al. 2013, Almeida et al. 2014, Reas et al. 2016), although often with a U-shaped finding, with more impairment among non-consumers and heavy consumers (Stampfer et al. 2005, Kim et al. 2016). A critical review has pointed out that due to heterogeneous definitions and classifications of alcohol drinking, and lack of separation between former drinkers and lifetime abstainers, no firm conclusions should be drawn (Ilomaki et al. 2015). This criticism is supported by a study showing a negative dose-response association between alcohol intake in midlife and subsequent cognition after excluding non-drinkers from the analysis (Hassing 2018). Also a negative association has been reported, especially related to heavy drinking (Gross et al. 2011, Woods et al. 2016). Given other

health concerns arising from drinking among older adults, there is insufficient evidence to promote alcohol consumption in order to reduce dementia risk (Piazza-Gardner et al. 2013), but it is possible that moderate consumption is not harmful for the brain (Panza et al. 2012).

Other foods and nutrients that have been associated with risk of dementia or cognitive impairment include nuts, olive oil, and coffee (Solfrizzi et al. 2017) and folate, vitamin E, carotenes, vitamin C, and vitamin D (Dangour et al. 2010, Balion et al. 2012, Rafnsson et al. 2013, Travica et al. 2017).

## **2.4 PREVENTION OF COGNITIVE DECLINE IN TRIALS**

### **2.4.1 PREVENTION IN THE CONTEXT OF DEMENTIA**

The potential for modifiable factors to prevent AD or dementia is huge, but estimates for their contributions vary. Up to one-third of AD cases could be prevented by reductions in diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity (Norton et al. 2014), even after accounting for non-independence between these factors.

Randomized controlled trials (RCTs) in prevention of cognitive impairment were initiated in the early 1990s often as ancillary analyses of large trials testing treatments for other conditions, such as blood pressure or hypercholesterolaemia, followed by pharmacological interventions with medications approved for treatment of AD (Andrieu et al. 2015). These studies with dementia as an outcome often failed to show an effect. The focus has subsequently shifted towards investigating cognitive trajectories and prevention of cognitive decline instead of dementia. Nutrition-related interventions started with nutraceuticals and dietary supplements and have progressed to dietary modification interventions in recent years.

Prevention is often divided into primary, secondary, or tertiary prevention. The goal of primary prevention is to reduce the incidence of the disease, typically before onset of the disease; secondary prevention aims to reduce progression of the disease from the early stages, typically among those with some signs of the disease; and tertiary prevention focuses on managing the disease and preventing complications. In the dementia context, alternative definitions for AD also shift concepts of primary and secondary prevention (Solomon et al. 2014). If the disease is considered to start with clinical symptoms, primary prevention occurs before the symptoms, but if onset is considered to occur when brain changes start to emerge, primary prevention would only occur at midlife and secondary prevention would take place already before clinical symptoms. In any case, there are no true thresholds between the types of prevention and preventive actions should be viewed as a continuous process parallel to disease development. Similar types of interventions may be effective in different

stages before the manifestation of full dementia, and at least currently, there is no evidence of optimal time windows for most interventions. Interventions among both cognitively intact participants and impaired individuals are reviewed here.

#### **2.4.2 DIETARY MODIFICATION**

Most of the dietary intervention trials reporting cognitive outcomes were not planned primarily for prevention of cognitive decline. Especially large-scale, long-term dietary intervention studies that provide only foods or counselling and have cognitive performance as a primary outcome are practically non-existent, and the most convincing findings come from studies with cognition as a secondary outcome.

The first meta-analysis of the trials testing MeDi identified five studies and concluded that the evidence was mostly non-significant (Radd-Vagenas et al. 2018). These trials were mainly of short duration (10 days to 24 weeks), with the exception of The PREvención con DIeta MEDiterránea (PREDIMED). The PREDIMED targeted primarily CVD, and assessed cognitive performance in subpopulations with somewhat varying results; over four years, the MeDi advice group with supplemental extra-virgin olive oil improved more in two out of seven tests and also their global cognition was significantly higher than the control group (Valls-Pedret et al. 2015). The MeDi advice group with supplemental nuts had a greater change in memory function. Previous results of this population reported better performance in cognitive tests after 6.5 years with MeDi+olive oil (Martinez-Lapiscina et al. 2013b) or better performance with either Medi+olive oil or MeDi+nuts than the control group (Martinez-Lapiscina et al. 2013a), but baseline cognitive assessment was not available in these sub-populations and change was not evaluated. Their study with a long-term intervention provides good-quality evidence of the effect of dietary modification, but due to the setting the role of MeDi advice in relation to supplemented foods remains unclear. The setting has been criticized for not being a pure test of MeDi guidance, olive oil, or nuts (Appel, Van Horn 2013).

In addition, a small trial has suggested that replacement of all vegetable oil with extra virgin olive oil may have cognitive benefits after one year (Mazza et al. 2018) compared with MeDi guidance alone. A DASH intervention combined with exercise was beneficial over 4 months for executive function and psychomotor speed, whereas the DASH group without exercise had better psychomotor speed only (Smith et al. 2010a), but these participants were middle-aged.

The longest duration dietary intervention with cognitive decline as a primary outcome was executed in Korean old age hostels, where dietary group counselling and menu changes improved dietary quality but were ineffective for cognition among older adults over a 33-month period (Kwok et al. 2012). Recently, a dietary intervention trial very similar to FINGER

reported improvement in cognition in the whole group and in dietary quality in the intervention group after one year, but no difference in cognitive function between the groups (Marseglia et al. 2018) with a tailored diet based on national recommendations of the participating countries. A small-scale pilot trial has suggested that calorie restriction would not be effective over 6 months alone or combined with exercise (Martin et al. 2007).

Modification of macronutrient composition in the diet has been mainly studied among middle-aged obese participants. A recent review including all trials that lasted longer than 24 hours (not post-prandial) in all age groups suggested that working memory, long-term memory, and attention could be sensitive to dietary manipulation, especially modification of energy and fat intake. However, there was considerable variability in outcomes and in methods of the trials, and the relevance of these effects in terms of dementia is unclear (Attuquayefio, Stevenson 2015). One trial among older adults reported a difference in processing speed after 8 weeks in favour of a high-carbohydrate low-fat diet compared with a ketogenic low-carbohydrate high-fat diet (Halyburton et al. 2007), but no longer after one year from the intervention (Brinkworth et al. 2009). In another study among MCI patients, better memory performance was reported in the very low carbohydrate group than in the high carbohydrate group in a 6-week trial (Krikorian et al. 2012).

### **2.4.3 DIETARY SUPPLEMENTS**

Most of the intervention trials to modify nutrient intake have been conducted with dietary supplements. A recent systematic review identified 20 RCTs containing >100 participants aged >65 years and with a follow-up of >1 year (D'Cunha et al. 2018). The most common interventions were supplementation with vitamins from the B group (B12 and folic acid alone or in combination) or omega-3 FAs, followed by combinations of nutrients, e.g. multi-vitamin supplements, and other single supplements such as ginkgo biloba. The most promising were trials testing vitamin B supplementation, which suggested benefits in the main analysis (Walker et al. 2012) or in subsamples with high homocystein (Oulhaj et al. 2016) or high omega-3 status (de Jager et al. 2012). One study showed a benefit of DHA supplementation in a subgroup (Quinn et al. 2010), but the overall evidence was not compelling. Despite high quality in terms of duration and size and specific age group, this review included studies in cognitively intact, MCI, and AD individuals and also studies with cognitive function as a primary or secondary outcome, thus yielding a heterogeneous group of studies.

After that review, a 24-month trial among participants with prodromal AD reported that a dietary supplement (medical food) that included several macro- and micronutrients was not effective for global cognition, but the cognitive-functional level detected by clinical dementia rating decreased less in the intervention group (Soininen et al. 2017). Protein-containing supplementary drinks have shown some benefit over 24 weeks for reaction

time, but not other for cognitive domains, among frail cognitively healthy older adults (van der Zwaluw et al. 2014) and for processing speed when combined with exercise (van de Rest et al. 2014).

Shorter term studies with fish oil supplements have also been inconclusive. One study reported that 900 mg/d DHA improved learning and memory function over 24 weeks in participants aged >55 years (Yurko-Mauro et al. 2010), but supplementation over 6 months was not beneficial among patients with MCI (Sinn N et al. 2012) or mild dementia (Freund-Levi et al. 2006), although the latter found some suggestion of an effect among those with very mild AD. A meta-analysis covering RCTs with DHA among adults of all ages with trial durations >1 month concluded that DHA appears to improve episodic memory in those with cognitive complaints, but not in those without (Yurko-Mauro et al. 2015). A concordant, earlier meta-analysis concluded beneficial effects of omega-3 supplementation among those with cognitive impairment, but not among healthy or AD patients (Mazereeuw et al. 2012). From a life course perspective, another meta-analysis suggests that benefits of omega-3 supplementation for cognition are evident only in infants, but no longer in middle-aged or older adults (Jiao et al. 2014).

Vitamins from the B group have also been investigated in many trials. A meta-analysis covering 11 homocysteine-lowering RCTs in all ages concluded no efficacy with supplementation of folate alone or with B<sub>12</sub> (Clarke et al. 2014), however, participants in these trials were typically not selected based on homocysteine levels. Supplementation with B<sub>12</sub> alone has also been concluded to be inefficient (Zhang et al. 2017).

Trials with vitamin E among those with MCI or AD showed no benefit (Farina et al. 2017), however, only a few heterogeneous trials were identified in this systematic review. Vitamin E was also ineffective in the general population with 8 to 10 years of supplementation (Kang et al. 2009, Kang et al. 2006), analogous to a trial with a multi-vitamin supplement including vitamin E over 7 years (Yaffe et al. 2004). In a similar setting where ancillary measures without a baseline cognitive assessment were executed, no effect of supplementation with betacarotene (Grodstein et al. 2007), a combination of B-vitamins (Kang et al. 2008), or a combination of B-vitamins and omega-3 (Andreeva et al. 2011) was found. However, one trial reported better subsequent episodic memory 6 years after the trial among those with multi-vitamin supplementation (Kesse-Guyot et al. 2011), and another showed a benefit in several cognitive domains after a 3-year supplementation with folic acid (Durga et al. 2007).

#### **2.4.4 PHYSICAL EXERCISE AND COGNITIVE TRAINING**

Physical exercise has been the most frequently tested lifestyle in intervention settings. A meta-analysis covering 18 RCTs concluded that a combination of aerobic and non-aerobic exercise or aerobic exercise alone resulted in a cognitive benefit among those with dementia, while non-aerobic exercise

alone did not (Song et al. 2018). The effect was seen for both AD and any dementia, and with higher or lower frequency of exercise. A previous meta-analysis, however, concluded that there was no evidence of a cognitive benefit with exercise in dementia patients, and only activities of daily living improved with the intervention (Forbes et al. 2015). Two meta-analyses suggest benefits in patients with MCI, one on global cognition (Song et al. 2018), while another only for verbal fluency (Gates et al. 2013).

A recent meta-analysis of 39 RCTs among >50-year-olds of varying cognitive status concluded that interventions of aerobic exercise, resistance training, multicomponent training, and Tai Chi all produced a significant benefit, and these results were consistent in all studied cognitive domains, and regardless of cognitive status (Northey et al. 2018). Previously, among those >50 years significant cognitive improvement was reported only for resistance training relative to stretching and Tai Chi relative to control, but no other differences and no overall effect were seen (Kelly et al. 2014b). Among cognitively healthy adults of any age, a meta-analysis with 12 trials found no evidence to support cognitive benefits of aerobic exercise (Young et al. 2015), in contrast to a previous analysis that covered all ages and did suggest benefits of aerobic exercise (Smith et al. 2010b).

One meta-analysis evaluating the effect of exercise in terms of dementia, MCI, or cognitive decline of “clinical significance” identified only five RCTs that did not support the efficacy of exercise in prevention (Barreto et al. 2017). However, of the two reviewed trials with cognitive decline as an outcome, one showed a benefit with higher adherence to exercise training (van Uffelen et al. 2008) and the other a positive overall effect (Muscari et al. 2010). Exercise interventions may also yield cognitive benefits in people with other chronic diseases such as arthritis, asthma, cancer, diabetes, or heart disease (Cai et al. 2017). Interventions related to diabetes are reviewed in more detail in the next section.

Meta-analyses of cognitive training (CT) have started to emerge in recent years. In patients with dementia, evidence suggests that training improves cognition (Huntley et al. 2015), however, not all improvements were considered clinically significant. For participants with MCI, a systematic review found most studies to show a modestly beneficial effect on memory with CT, but not all of these studies were RCTs (Gates et al. 2011). Among cognitively intact participants, the most recent meta-analysis covered 31 RCTs and concluded that training had a moderate positive effect on total cognition and executive function, and a small effect on all other domains in trials lasting >5 weeks among >65-year-olds (Chiu et al. 2017). Training more frequently, longer, and with more sessions may yield a greater effect size. A previous analysis of any CT or mental stimulation also found an effect on global cognition and executive function (Kelly et al. 2014a), and moreover this study suggested that training was associated with better subjective memory and that group training may produce more benefit than individual training. When computerized training only was analysed, training was

modestly effective in improving memory, but not executive function or attention (Lampit et al. 2014). Furthermore, unsupervised home training appeared ineffective, and training more than three times a week provided no additional benefit.

One meta-analysis investigated the effect of either aerobic exercise or CT among cognitively healthy adults aged >55 years and concluded that both extended practice and aerobic fitness produced a significant training effect, and their effect sizes are similar in magnitude (Hindin, Zelinski 2012). A meta-analysis of interventions combining PA and CA in patients stated that combined interventions appear to improve global cognition in both AD and MCI (Karssemeijer et al. 2017).

#### **2.4.5 DIABETES PREVENTION AND CONTROL**

Current literature shows relatively constantly that people who remain free of diabetes have a lower risk of dementia and cognitive decline, but less is known about the possibilities of modifying that risk with either prevention or control of diabetes. Because differences in cognitive decline over time between those with and without diabetes appear modest, chances to detect treatment effects may be small (Biessels et al. 2014). No studies that were primarily planned to investigate prevention of cognitive decline with intervention to prevent or control diabetes are available, and evidence comes from studies that have added cognitive measures as secondary outcomes, which may further hinder the possibilities of detecting treatment effects. A recent review concluded that, in general, prevention of diabetes with diet and exercise reduces or delays diabetes, but there is no evidence of prevention of associated complications such as cognitive impairment (Hemmingsen et al. 2017).

Intensive treatment of diabetes with a combination of lifestyle changes and medication did not result in cognitive benefit immediately after the 4-year intervention (Launer et al. 2011) or after an additional follow-up to 7 years (Murray et al. 2017). After 4 years, a small but significant difference in brain total volume was detected in favour of the intervention, but this difference vanished in the later follow-up. An intensive 4-year weight-loss intervention among overweight and obese participants with diabetes resulted in no difference in cognitive function 10 years after the randomization (Rapp et al. 2017, Hayden et al. 2017a) and even small decrements in cognitive change between 10 and 15 years of follow-up were observed (Espeland et al. 2018), especially among obese participants. A smaller trial targeting lifestyle intervention to screen-detected diabetes also showed no benefit over 6 years (Koekkoek et al. 2012).

As for individual lifestyles, a systematic review of exercise trials with six studies (including substudy II of this thesis) concluded that there was no evidence supporting the contribution of PA interventions to better cognitive function among those with diabetes or IGT, however, the studies included

were inconsistent and only three were RCTs (Zhao et al. 2018). It is noteworthy that the two trials measuring cognition during the intervention did show a positive effect with a 6-month exercise intervention among older adults with IGT (Baker et al. 2010) and with a diet and exercise intervention at 6 months but no longer at 12 months (Watson et al. 2006). Most studies have been unable to evaluate changes during the intervention due to lack of baseline cognitive assessment.

Prevention of diabetes among those with high risk based on overweight and elevated glycaemia has proven successful (Knowler et al. 2002, Tuomilehto et al. 2001), and this appears to be a long-term effect (Lindstrom et al. 2013, Nathan et al. 2015). Diabetes prevention has not, however, been reflected in cognitive functions, with no difference between the intensive lifestyle intervention group and the control group in the DPS 13 years after the randomization in CERAD-TS or TMT-A (Luchsinger et al. 2015), and no difference between the intensive lifestyle intervention or metformin group and the control group in the US Diabetes Prevention Program after a 12-year follow-up in composite score of four tests or on any individual test (Luchsinger et al. 2017).

Lack of statistical power in ancillary analyses, lack of baseline cognitive assessment, and relatively short follow-up times in fairly young populations may explain the non-significant associations between treatment/prevention of diabetes and cognitive function. Currently, there is no evidence to support modification of risk for dementia or cognitive impairment through diabetes prevention or treatment.

#### **2.4.6 WEIGHT LOSS**

The two-way relationship between weight and dementia discussed in Section 2.2.3 underlines the importance of distinguishing between intentional and unintentional weight loss, which is usually not possible in observational studies. Some RCTs are available to evaluate effects of weight loss on cognitive function, although most of these included middle-aged participants. A recent meta-analysis reported improvement in memory, attention, and executive function after weight loss (Veronese et al. 2017), concordant with an earlier report (Siervo et al. 2011). Both of these analyses included adults of all ages, and only two trials were identified with populations aged >60 years; one showed a benefit of exercise alone or in combination with a weight-loss diet over 1 year (Napoli et al. 2014) and the other a benefit of caloric restriction over 3 months (Witte et al. 2009). The relevance of subtle cognitive changes in midlife in terms of dementia risk is unclear. An earlier meta-analysis including only participants aged >65 years concluded that despite the successful weight change there was no evidence to support weight loss among older adults in terms of cardiovascular risk factor or mobility improvement (Witham, Avenell 2010), but none of the reviewed studies assessed cognitive function.



#### **2.4.7 MULTIDOMAIN INTERVENTION TRIALS**

A history of many failed studies focusing on a single factor and improved understanding of the multifactorial aetiology of late-life cognitive impairment initiated the idea of multidomain interventions targeting several lifestyle factors simultaneously. Such intervention trials have been recommended as a research priority (Downey et al. 2017).

A systematic review in 2013 identified six completed multidomain studies and eight ongoing studies; three of the completed ones investigated a combination of PA and CT, two nutritional supplements with exercise, and one dietary intervention (Schneider, Yvon 2013). This review suggested that targeting multiple factors may be more effective than targeting a single factor.

Since this review, three large multidomain interventions primarily planned to prevent cognitive decline or dementia have been completed. The Finnish FINGER trial (analysed in substudies III and IV) showed a beneficial effect on cognition with an intervention comprising dietary counselling, exercise, cognitive training, and monitoring of cardiovascular risk factors over 2 years among a population at risk for dementia (Ngandu et al. 2015). Benefits were seen in global cognition and in executive function and processing speed. The French MAPT trial tested a multidomain lifestyle intervention alone or combined with an omega-3 supplement for 3 years among participants with subjective memory complaints, limitations in instrumental activities of daily living, or slow gait speed, but found no overall benefit of any intervention (Andrieu et al. 2017). In post-hoc analysis, the combined intervention (lifestyle+omega) appeared beneficial among those with a higher risk of dementia, and lifestyle interventions with or without omega among those with baseline amyloid-positive PET scans. The Dutch PRE-DIVA was a cluster-randomized, nurse-led, multidomain cardiovascular intervention trial, including medication for vascular risks, with dementia incidence over 6 years as an outcome. The intervention did not reduce the incidence of dementia in the main analysis, but again, in a subgroup with untreated baseline hypertension a significant difference between groups emerged in both hypertension and dementia incidence (Moll van Charante et al. 2016).

Two pilot intervention studies have been published, one suggesting that a multidomain goal-setting intervention including exercise, social activities, and diet may be beneficial for at least one year (Clare et al. 2015) and the other that an intervention focusing on PA and cognitive stimulation is beneficial among those with MCI over 12 weeks (Dannhauser et al. 2014). Also, a small trial with a holistic health approach yielded cognitive benefits over 10 weeks (Young et al. 2017), with an intervention that promoted enhancement of memory and coping skills and development of a positive lifestyle, positive emotions, and emotional support, and also more traditional interventions like dietary improvement, physical exercise, and recreational activities. Conversely, a Finnish multidomain intervention, which aimed

primarily at prevention of CVD, found no difference in cognition after 2 years of intervention with diet, aerobic exercise, or resistance training alone or in combinations (Komulainen et al. 2010). This was only an interim analysis of a 4-year trial, but the statistical power in comparing six distinct groups may be limited also after a longer intervention.

One systematic review summarized that among frail older adults the evidence of cognitive benefits of multidomain interventions is limited, but increasing (Dedeyne et al. 2017).

## **2.5 METHODOLOGICAL CONSIDERATIONS**

### **2.5.1 DIETARY ASSESSMENT**

Measuring usual dietary intake remains a challenge in nutritional epidemiology, and especially methodological studies among older populations are scarce. In general, there is high day-to-day and also seasonal variation in dietary intake, and both recall of foods eaten and portion size estimation are prone to many errors. Self-reports of diet may yield over- and underreporting, causing systematic or unsystematic error. Furthermore, the data collection methods, such as food record and food frequency questionnaire (FFQ), are demanding for both participants and researchers.

For collecting dietary intake data, the FFQ (either quantitative or semi-quantitative) is considered the best estimate of long-term diet for epidemiological studies, and it is most commonly used also in studies of cognitive performance. Food records remain the gold standard for measuring dietary intake, and records or 24-h interviews are likely to capture changes in diet better (Willett 2013). In addition to the costly and time-demanding nature of the food record method, the main disadvantage is estimation of usual intake, which requires over 7 days of recording for many nutrients (Willett 2013). With food records, intake tends to be underreported, whereas with FFQ overreported intakes are more common.

The most suitable methods for dietary assessment among older adults are unknown. It has been suggested that as older persons differ from each other with respect to the abilities needed for dietary assessment the best methods may differ too (Volkert, Schrader 2013). Validity of food records is not well known in older adults since records have usually served as the reference method in validation studies (Schroder et al. 2011, Eysteinsdottir et al. 2012). Underreporting in food records has been demonstrated among older adults with low education or higher BMI (Luhrmann et al. 2001). However, a study using FFQ suggested that under-eating also occurs among older adults, and it should not be perceived as underreporting (Shahar et al. 2010).

The effect of age and possibly declining cognition on dietary reporting has not yet been elucidated is not yet well known. Typically, the same methods and questionnaires are used as with younger participants, but lower cognitive

ability has been associated with reporting errors in FFQ (Pope et al. 2007), and lower executive functions with bias in repeatability and validity of FFQ (McNeill et al. 2009). No data estimating the reliability of food records among those with lower cognitive performance exist.

## **2.5.2 DESIGN CONSIDERATIONS**

As reviewed in previous sections, studies that evaluate the role of diet and lifestyle in the development of cognitive impairment are abundant. Still, very few associations are consistent across studies, and in most meta-analyses evidence is regarded as weak. In addition to difficulties in measuring cognitive function and dietary intake, there are various methodological challenges related to study design when it comes to investigating prevention of dementia or cognitive decline.

Randomized controlled trials, which are considered the gold standard in the chain of scientific evidence, may also be misleading if not designed properly; and it is particularly challenging to execute RCTs for a condition that perhaps might need an intervention in midlife in order to demonstrate effects in later life (Richard et al. 2012). Many issues have been identified in previous RCTs, e.g. missing the optimal time window, inadequate follow-up times, suboptimal outcome measures, focus on individual interventions instead of multidomain approaches, and inappropriate control groups (Downey et al. 2017). Any of these reasons alone or together may lead to lack of statistical power and misinterpretations of the effect.

However, methodological improvements are ongoing in trials, and more evidence has started to accumulate. In 2010, report by the US National Institute of Aging concluded that although there was some support of the deteriorating role of diabetes, ApoE4, smoking, and depression and the protective role of cognitive engagement and physical activities, there was still insufficient evidence to support any recommendations for prevention of AD (Williams JW et al. 2010). An updated version in 2017 concluded that interventions of cognitive training, blood pressure management for people with hypertension, and increased PA are supported, although the evidence is inconclusive (Downey et al. 2017).

Most of the trial evidence to date is drawn from studies adding cognition as a secondary endpoint. Such designs are of importance when no primary studies are available, but negative findings should be interpreted with caution. Most of these trials with ancillary cognition assessments have not established power calculations related to cognition, and hence, negative results can be interpreted as either no association or lack of statistical power. Some reviews and meta-analyses exclude such studies (Andrieu et al. 2015), but most do not.

In terms of prospective studies, design considerations are as abundant. Outcomes include cognitive test results as continuous variables, changes in cognition over time as continuous variables, falling below a certain threshold

such as definition for MCI, or categorization as having declined versus not declined over time. All of these studies can be conducted in cognitively healthy, mildly impaired, or demented populations, or a mixture of any status with a wide range of follow-up times. Furthermore, development of either AD, VaD, or any dementia may serve as outcomes and also conversion from MCI to dementia. When cognitively healthy participants are included, their age is not always restricted to older adults, and especially with short-term studies, their relevance for dementia prevention is unclear.

When assessing the associations between diet or lifestyle with cognition in older age, the impact of reverse causation needs to be taken into account, i.e. preclinical AD may cause changes in measured risk factors. For many of the CVD risk factors, such as blood pressure, BMI, and cholesterol, risk ratios appear to turn in the opposite direction between midlife and older age, which is speculated to be at least partly due to reverse causation (Sajeev et al. 2016, Tolppanen et al. 2012). For example, high BMI >20 years before the dementia diagnosis increases risk of dementia, 10-20 years before diagnosis there is a borderline significant association, and a clear benefit of higher BMI is present 10 years before the diagnosis, supporting the reverse causality hypothesis already a decade before the diagnosis (Kivimaki et al. 2018).

### 3 AIMS

The general objective of this study was to investigate the role of diet, physical activity, body weight, glycaemia, and changes in the forementioned in the development of cognitive decline within a lifestyle intervention trial in midlife and in older adulthood.

Specific study aims were as follows:

- I. To investigate how incident diabetes, duration of diabetes, and long-term glycaemia are associated with subsequent cognitive performance.
- II. To evaluate whether dietary fat and fibre intake, physical activity, body weight, and changes in the forementioned from midlife to older age are associated with subsequent cognitive performance.
- III. To analyse the success of a dietary intervention among older adults in terms of changes in overall diet quality (pre-specified secondary outcome of the trial) and to describe how dietary guidance affects nutrient intakes and food consumption.
- IV. To examine how diet quality and dietary changes are associated with cognitive changes over two years among older adults within a multidomain lifestyle intervention.

## 4 METHODS

This study is based on data from two main studies, namely the Finnish Diabetes Prevention Study (DPS) (Substudies I and II) and the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Substudies III and IV). Both were randomized, controlled, multicentre, multidomain lifestyle intervention trials with a successful treatment effect related to the primary outcome, diabetes in the DPS (Tuomilehto et al. 2001) and cognitive decline in the FINGER (Ngandu et al. 2015). Substudies I, II, and IV are ancillary analyses, whereas Substudy III includes a pre-specified secondary outcome analysis.

### 4.1 SETTING IN THE DPS (I,II)

The DPS aimed at prevention of type 2 diabetes among middle-aged adults at risk for diabetes (Eriksson et al. 1999). An active intervention period was conducted between 1993 and 2000 and was extended with a follow-up phase. An ancillary cognition study was added in 2009 to the protocol and repeated in 2011. Everyone who participated in the original intervention period and had not withdrawn was invited to the cognition study at both rounds. The trial was registered with the ClinicalTrials.gov (no. NCT00518167).

Participants were middle-aged at the time of recruitment (range 40 to 65 years at randomization), overweight or obese (body mass index  $>25$  kg/m<sup>2</sup>), and all had IGT at baseline defined by the mean of two oral glucose tolerance tests (OGTTs). The 522 subjects were randomized into two groups; the intervention group (n=265) received individualized dietary, exercise, and weight reduction counselling, whereas the control group (n=257) received only general health advice. The intervention group received frequent individualized dietary, PA, and weight reduction counselling, which has been described in detail previously (Lindström et al. 2003). Counselling included seven meetings with the study nutritionist during the first year and once every three months thereafter. Supervised exercise sessions at the local gym were offered.

The five main goals of the DPS intervention were weight reduction of 5% or more, less than 30% of energy from fat, less than 10% of energy from SFA, dietary fibre intake of  $>15$  g/1000 kcal ( $>3.6$  MJ), and moderate intensity PA at least 30 min/day. Weight loss was measured annually at the study visits by the study nurse, and other goals are self-reported estimates of independent lifestyles at home.

Development of diabetes was monitored annually, and if a participant developed diabetes, the intervention was discontinued, but the participant was later invited to follow-up visits. Lifestyles were assessed annually

throughout the intervention period and bi-annually during the follow-up, resulting in 3-6 measures during the intervention and 1-6 measures during the follow-up (before the cognition study) for each participant.

The intervention period was planned to continue for 6 years, but it was prematurely discontinued based on interim endpoint analyses showing a significant difference between the groups in diabetes incidence. The duration of the intervention thus varied, with an average of 4 years. Achievement of goals during the intervention was assessed after 3 years since not all participants had a longer intervention.

## **4.2 SETTING IN THE FINGER (III, IV)**

The FINGER aimed at prevention of cognitive decline among older adults at risk for dementia (Kivipelto et al. 2013). Recruitment and the 2-year intervention period were executed between 2009 and 2014, and follow-up of at least 7 years is ongoing. This trial is registered with the ClinicalTrials.gov (no. NCT01041989).

Participants in the FINGER were recruited from previously conducted randomly selected observational surveys, hence comprising a population-based sample. The dementia risk score (Kivipelto et al. 2006) was calculated based on previous data, and participants aged 60-77 years and with at least a slightly elevated risk (>6 points) were invited to participate from six areas. At screening, an inclusion criterion was cognitive performance at a mean level of slightly lower than expected for age at the CERAD test battery (Morris et al. 1989), defined as (1) Word List Memory Task (10 words)  $\leq 19$  words, (2) Word List Recall  $\leq 75\%$ , or (3) MMSE between 20 and 26 points out of 30. The 1260 participants recruited were randomized into the multidomain intervention (n=631) or control (n=629) receiving general health advice. The FINGER multidomain intervention was more complex compared with the DPS, and all of the intervention sub-domains had their own goals.

The goals of the dietary intervention were based on national dietary recommendations (National Nutrition Council 2005), but nutrient intakes were translated into food-level goals. Goals communicated to the participants were increasing consumption of fruit and vegetables (>400 g/d), choosing whole-grain cereal products instead of refined ones, changing to low-fat options in milk and meat products, limiting sucrose intake to <50 g/d, using vegetable margarine and rapeseed oil, and consuming fish at least two times per week.

Because of the age group, weight loss attempts were always carefully considered after taking individually into account BMI, health status, age, and diet of the participant. If considered safe and necessary, energy intake facilitating a 5–10% reduction in body weight was recommended and prevention of unintentional weight loss was also monitored.

The dietary intervention was based on the theoretical guidelines to intervention planning approaches (Bartholomew et al. 2000). Although national dietary recommendations were listed as the goal for intervention, all goals were translated into concrete food-level goals and further to individual behaviour. The dietary intervention was carried out as a combination of individual (3 sessions) and group counselling (6-8 sessions depending on the centre), and it was more intensive during the first year. Vitamin D supplement was recommended to all participants in FINGER, including the control group, following the national guidelines. The dietary intervention is described in detail in Substudy III.

The physical exercise domain was based on international guidelines (Nelson et al. 2007), and the programme was a modified version of the DR's EXTRA study protocol (Komulainen et al. 2010). Muscle strength training at the local gym was offered, guided by physiotherapists during the first 6 months. Training was progressive and the goal after the first 6 months was 2-3 sessions of strength training weekly, accompanied by individual aerobic exercise. The programme was regularly adjusted with the physiotherapist.

The cognitive training domain exploited an internet-based computer program, which was first introduced during group meetings by a psychologist (6 meetings). The computer training includes two periods of independent training of 6 months each, when participants train using the cognitive training program three times/week, 10-15 min/session, for a total of 72 training sessions per period. Computer tasks were progressive in difficulty, although the amount and structure of tasks remained similar throughout the training.

For the monitoring and maintenance of metabolic and vascular factors, participants met the study nurse once every 3 months during the first year and once every 6 months during the second year for risk factor evaluation and motivation. They also received feedback from their laboratory measures and other measures taken during the study, and met the study physician at the beginning and the end of the intervention, and 2-3 times in between. No medications were prescribed in the study and participants were advised to contact their own physician if needed.

### **4.3 ETHICAL ISSUES**

The original DPS study protocol for the intervention period was approved by the ethics committee of the National Public Health Institute in Helsinki, and the protocol for the follow-up period and the cognition study by the ethics committee of the North Ostrobothnia Hospital District. All participants gave written informed consent at baseline, at the beginning of the post-intervention follow-up, and at the beginning of cognitive assessments.

The FINGER study has been approved by the coordinating ethics committee of the Helsinki and Uusimaa Hospital District (94/13/03/00/09).



The participants gave their written informed consent before enrolment. The principles of good clinical and scientific practice were applied in both studies according to the guidelines laid down in the Declaration of Helsinki.

#### **4.4 COGNITIVE ASSESSMENT (I, II, IV)**

Cognitive functions in the DPS cognition study were evaluated with a validated Finnish translation of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery (Morris et al. 1989) and Trail Making Test A (TMT) performed by trained study nurses. The CERAD battery is composed of (1) Verbal fluency (naming as many animals as possible in 1 min), (2) Modified Boston Naming test (15 words), (3) Mini-Mental State Exam, (4) Word List Memory (learning of 10 words, three trials), (5) Constructional praxis (copying four figures out of a model), (6) Word List Recall (delayed recall of the ten words presented in the word list memory task), (7) Word List Recognition (recognition of the previous 10 words out of 20 words), (8) Constructional praxis recall (drawing the previous four figures, later and without a model), and (9) Clock drawing. We calculated the CERAD total score (CERAD-TS) to measure overall cognitive performance (Chandler et al. 2005). The TMT was calculated as time in seconds without an upper limit (longer time indicating worse performance).

Cognitive function in the FINGER was evaluated with an extensive neuropsychological test battery (NTB) (Harrison et al. 2007), performed by trained study psychologists. The global cognitive function is defined as the NTB total score, a composite score based on results from 14 tests (calculated as Z scores standardized to the baseline mean and SD, with higher scores suggesting better performance). Separate NTB domain Z scores were calculated for executive functioning, processing speed, and memory. The executive functioning domain included category fluency test, digit span, concept shifting test (condition C), trail making test (shifting score B – A), and a Stroop test interference score. The processing speed domain included letter digit substitution test, concept shifting test (condition A), and Stroop test (condition 2). The memory domain included visual paired associates test, immediate and delayed recall, logical memory immediate and delayed recall from Wechsler Memory Scale-Revised/III, and word list learning and delayed recall from the CERAD battery. MMSE was annually performed by the study nurse.

## **4.5 DIETARY ASSESSMENT (II, III, IV)**

Dietary intakes were collected with a 3-day food record in both studies. In the DPS, records were collected annually four times during the active intervention phase (baseline, years 1, 2, and 3), and twice during the follow-up. In FINGER, three records were collected close to annual visits (baseline, years 1 and 2). Records were checked face-to-face with the participant by either the study nutritionist (DPS) or a trained nurse (FINGER). Participants received written instructions on how to record all foods and beverages consumed, including the type, brand, and preparation method, with household measures. Recording was facilitated with a picture booklet.

Dietary data were recorded by trained nutritionists and analysed using a software program developed at the Finnish National Public Health Institute and the Finnish food composition database (Ovaskainen et al. 1996) in the DPS and a more advanced version of the same program at the National Institute for Health and Welfare in the FINGER (National Institute for Health and Welfare, Nutrition Unit Helsinki 2011). The program allows modification of standard recipes, and personal recipes were used whenever available (recording e.g. the type of fat used in cooking). Foods and beverages were categorized and summarized into main categories, and intakes and consumption was calculated as the mean over 3 days (or less, if not all days were available).

## **4.6 ASSESSMENT OF OTHER LIFESTYLES AND COVARIATES (II, III, IV)**

Annual study visits in both studies included a physical examination with measurements of height (without shoes), weight (in light indoor clothes), waist circumference, and blood pressure, and fasting blood samples were collected, including OGTT (for those without diabetes diagnosis). Body mass index (kg/m<sup>2</sup>) was calculated. Participants filled in health questionnaires, and medical history was obtained via interview by the study nurse (DPS) or physician (FINGER). Frequency and intensity of PA were ascertained with modified versions of a validated questionnaire to assess annual leisure-time PA (Taylor et al. 1978, Lakka, Salonen 1992, Lakka et al. 1994) in both studies. Cognitive and social activities in FINGER were collected with a questionnaire enquiring about weekly frequency of reading, crosswords, writing, games, music, communal activities or participation in societies, studying, handicrafts, gardening, cleaning, baby-sitting, and voluntary work.

## **4.7 DIABETES AND GLYCAEMIA (I)**

In the DPS, annual study visits comprised a 2-h OGTT. Diabetes was diagnosed according to the WHO criteria from 1985 (World Health Organization 1985) as either fasting plasma glucose of 7.8 mmol/L or more, or 2-h plasma glucose of 11.1 mmol/L or more at OGTT. The diagnosis was confirmed by a repeat test. Diabetes diagnoses until the first cognitive assessment were used to determine diabetes status in Substudy I.

In FINGER, self-reported diabetes at baseline was used to compare the populations in the Results section of this summary, but these data were not analysed in this study. Those who reported having been diagnosed by a doctor with type 1 diabetes, type 2 diabetes, or diabetes of unknown type (but not gestational diabetes) were categorized as having diabetes. Fasting samples and OGTT (for those not reporting diabetes) were also collected annually, but these data were not used in this study.

## **4.8 DEFINITIONS FOR INTERVENTION GOALS (II, III, IV)**

The DPS had five main goals, including weight loss, decrease in total fat and SFA intake, increase in fibre intake, and moderate-intensity PA (Table 3). Dietary variables were calculated from diet records, weight change was measured at the annual visits and the change calculated each year relative to baseline, and exercise was reported in the health questionnaire with a four-category question of usual weekly frequency of PA. These were defined based on the mean value of three measures during the intervention phase (years 1-3) for continuous variables and median for categorical (exercise) variable. A total score in the range of 0-5 was calculated.

In the FINGER dietary intervention, adherence was measured with nine distinct goals, including six nutrient goals, i.e. intakes of SFA, PUFA, protein, fibre, sucrose, and alcohol, and three food-related goals, i.e. consumption of vegetables, fruits, and fish (Table 3). Both nutrient and food intakes were drawn from food records and defined as the mean of three days. Goals were defined annually and annual dietary adherence score was calculated with a possible range of 0-9. Achievement of goals related to other intervention domains was not evaluated in this study. Intervention goal achievement was defined for the control group as well in both studies.

## **4.9 STATISTICAL METHODS**

In both studies, differences between background characteristics were compared with t-test (continuous variables between two independent samples) or  $\chi^2$ -test (categorical variables) as appropriate.

**Table 3.** Dietary intervention goals in the FINGER and all intervention goals in the DPS.

DPS		FINGER	
Components	Criteria for 1 point	Components	Criteria for 1 point
SFA	<10E%	SFA and trans-FA	<10E%
Total fat	<30E%	PUFA	5–10E%
Fibre	>15 g/1000 kcal (~4.2 g/MJ)	Fibre	>3 g/MJ
Weight loss	5% of baseline weight	Sucrose	<10E%
Physical activity	>30 min/day moderate intensity	Protein	10–20E%
		Alcohol	<5 E%
		Fish and shellfish	Any consumption (during 3 days) <sup>1</sup>
		Vegetables	>200 g/d
		Fruit and berries	>200 g/d
Score total	0-5	Score total	0-9 p

E%, proportion of total energy intake.

<sup>1</sup> Goal for the participants is twice a week, but in the analyses any consumption (in a 3-day food record) is used as a surrogate for this goal.

#### 4.9.1 ANALYSES OF ONE OR TWO ASSESSMENTS (I, II)

In the DPS, two repeated measures of cognitive assessment were available, which were measured 9 and 11 years after the intervention period. Significance of change in cognitive function between the assessments was tested with paired t-test in the whole group and in each diabetes group separately (I). Otherwise, linear regression modelling was applied in all of the DPS cognition analyses (I,II), with cognitive performance or change in cognitive performance as an outcome and appropriate covariates in the model. For each participant, the first available cognition assessment was chosen (either round 1 or round 2) to represent the overall level, and change in cognitive performance was calculated as the difference between the two assessments for those participating twice.

Separate means were calculated for glycaemia variables for the intervention period (1-4 years) and the post-intervention follow-up (5-13 years) in Substudy I. An overall mean was calculated for total fat, SFA, fibre intakes, BMI, and exercise over the whole study period (intervention and

follow-up, 13 years) in Substudy II. Change over time in predictors was determined as the difference between the overall mean value and the baseline value. Furthermore, weight change profiles were analysed as factor variables (II), when separate means were calculated for the active intervention phase and for the follow-up phase for BMI and waist circumference. Weight change categories were determined as weight loss versus weight gain during the intervention phase, then as loss versus gain from the intervention to the follow-up phase, and their combination. Cognitive scores were skewed to the right, and Box-Cox transformation (Box, Cox 1964) was applied. Differences between the models were modest, and coefficients presented are from non-transformed models to improve interpretation. Analyses were executed with Stata for Windows, release 11.2 (StataCorp LP).

#### **4.9.2 ANALYSIS OF THREE REPEATED ASSESSMENTS (III)**

In the FINGER, three repeated assessments of cognition and dietary intake were performed, diet being the outcome in Substudy III. Linear mixed models were executed, with time as a random factor, dietary adherence score or each nutrient as an outcome, and group allocation and time as predictors without confounding variables (pre-specified secondary outcomes of the trial). The interaction term group\*time represented the difference in change between the groups. Time was entered as a factor variable to allow non-linear change over time (based on better model fit), and hence, the difference was estimated separately for the first and the second year. Within-group changes were also estimated from mixed models (linear combinations –lincom– in Stata). Zero-skewness log transformation was applied for dietary intakes to improve normality, and statistical comparisons were obtained from these models. Coefficients for intake are untransformed in tables to facilitate interpretation.

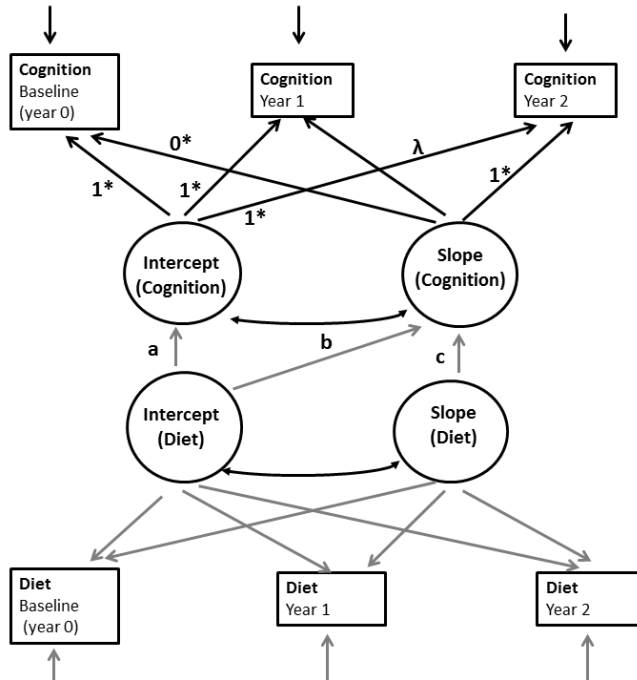
To estimate the role of each individual dietary goal in the Results section of this summary, a similar mixed model was applied for the cognition data, with time as a random factor, total composite cognition score as the outcome, baseline adherence to each intervention goal as predictor with time, and age, education, sex, BMI, LDL cholesterol, systolic blood pressure, baseline PA, baseline CA, and total energy intake as covariates. Analyses were executed with Stata for Windows, release 11.3 (StataCorp LP).

#### **4.9.3 ANALYSIS OF PARALLEL GROWTH CURVES (IV)**

The association between two variables that both change over time was analysed in Substudy IV, where parallel latent growth curve analysis within the structural equation modelling context was applied. Latent variables for general level (intercept) and change (slope) of both diet and cognition over the study period (baseline, 1st and 2nd year) were estimated (Figure 3).

Growth curve analyses were executed by groups based on intervention allocation using `-group-` option in Stata, allowing determination of which parameters can be estimated as equal between groups. Analyses were initiated with a theoretical full path model (Model 0) and parameters were constrained as equal between groups one at a time, each model compared with the full model using likelihood ratio test as follows: Model 1) Best model based on univariate models (shape parameters, measurement error variances. and constant of diet estimated as equal between groups); Model 2) Measurement error covariance estimated as equal; Model 3) constant for cognition estimated as equal; Model 4) intercept (diet)→intercept (cognition) estimated as equal; Model 5) intercept (diet) → slope (cognition) estimated as equal; and Model 6) Path slope (diet)→ slope (cognition) estimated as equal between groups, i.e. all parameters estimated as equal between groups as if there were only one similar group. The final model was considered to be Model 6, if all constraints were allowed. Model 3 is presented in the results also in order to capture differences in associations between groups, which are of interest due to intervention setting. An additional constraint was tested by dropping the path between latent slopes, i.e. Model 7) slope (diet) → slope (cognition) constrained to [0], to determine the effect of baseline diet on cognitive change when dietary change was not taken into account.

Time was non-linear for both diet and cognition based on best fit in univariate models, by not constraining the factor loading for latent slope of the middle year [0, free, 1]. Factor loadings for latent intercept were constrained to [1,1,1]. Analyses were executed with Stata SE 15.1 for Windows (StataCorp LP).



**Figure 3.** Graphical presentation of the parallel latent growth curve model.

a) Refers to the path examining the cross-sectional associations of baseline (intercept) diet with baseline (intercept) cognition (Baseline diet→Baseline cognition in Table 9), b) refers to the path examining the prospective association of baseline (intercept) diet with change (slope) in cognition (Baseline diet→Cognitive change in Table 9), and c) refers to the parallel associations of changes in diet with change in cognition (Dietary change→Cognitive change in Table 9).

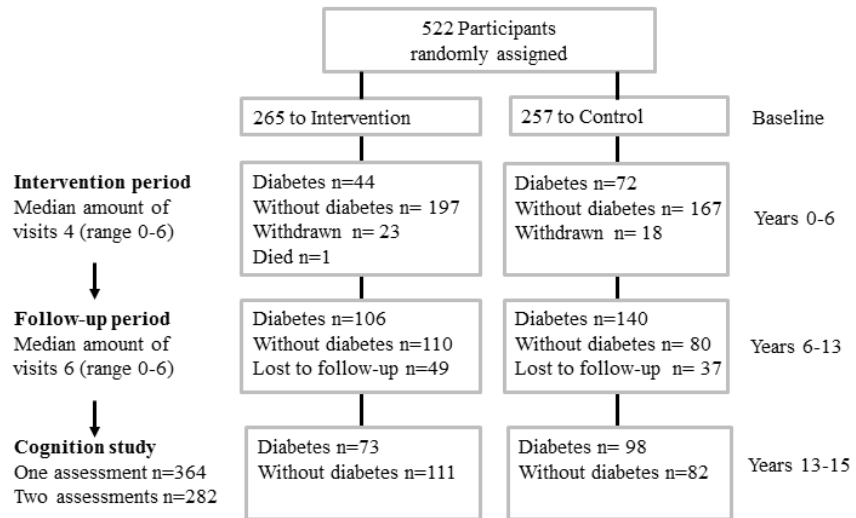
## **4.10 PARTICIPANTS AND THEIR CHARACTERISTICS**

Characteristics for both study populations are presented in Table 4 and flowcharts in Figures 4 and 5. Of the original DPS cohort, 70% (n=364) participated in the cognition assessment at least once (either the first or the second assessment) and 54% (n=282) twice. Mean age at the first assessment was 68 (range 52 to 82) years. Among those with diabetes, time since the diagnosis was longer for non-participants ( $p=0.005$ ). Altogether 26 DPS participants had died before the first cognitive round (5% of the whole cohort; 16% of non-participants).

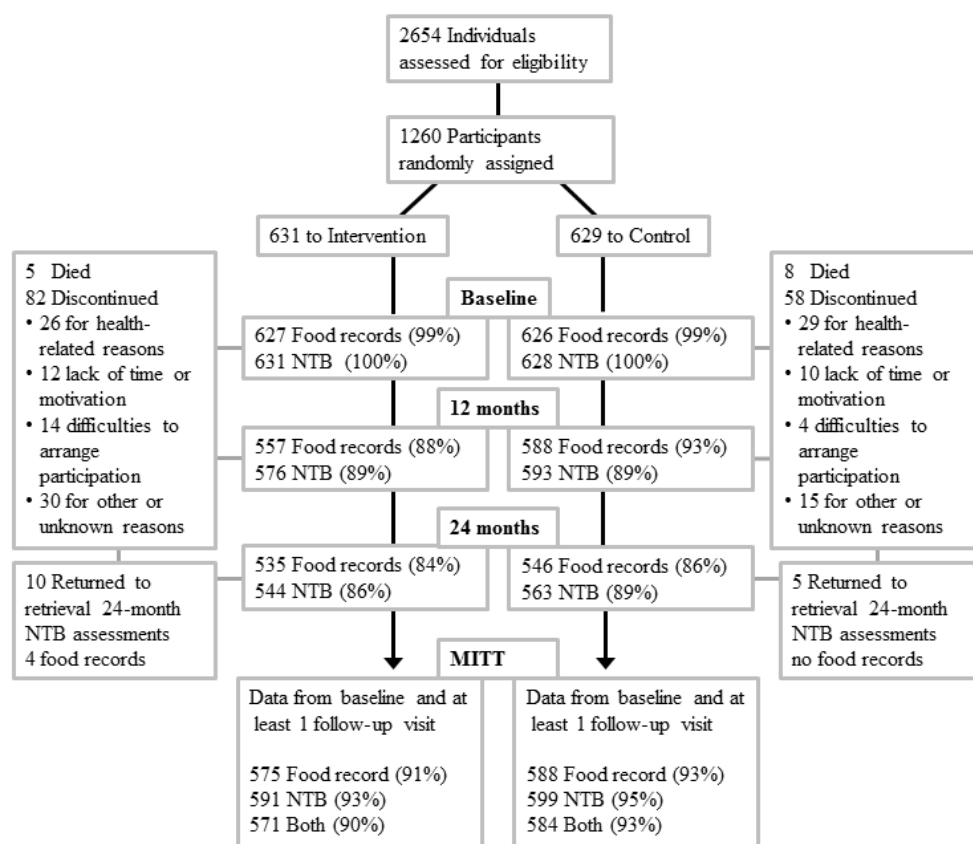
In the FINGER, no differences were present between the intervention and control participants. Mean age at baseline was 69 (range 60-77) years. Participants who were not included in the MITT analysis were mostly drop-outs, with only the baseline assessment. During a 2-year period 150 participants withdrew from the study (12%), 13 (1%) of whom had died. The most common reasons for dropping out were health-related (n=55) or lack of time or motivation (n=22).

Both populations were selected based on elevated risk: elevated risk for diabetes in the DPS and elevated risk for dementia in the FINGER. The populations were similar in terms of mean age at the cognition study, but the range was wider in the DPS. While the DPS participants were subjected to the lifestyle intervention during midlife and cognition was assessed years after the intervention period, the FINGER participants were recruited in later adulthood and cognitive functions were assessed simultaneously during the intervention period. In the DPS, participants were unselected regarding cognition, while in the FINGER those with the highest and lowest scores were excluded. The DPS intervention lasted on average 4 years compared with 2 years in the FINGER.





**Figure 4.** Flowchart of the Diabetes Prevention Study from baseline to ancillary cognition assessments (I,II).  
Diet records collected three times during the intervention and three times during the follow-up.



**Figure 5.** Flowchart of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (III,IV). NTB, neuropsychological test battery. MITT, modified intention to treat (those with baseline and at least one of the follow-up measure).

## 5 RESULTS

### 5.1 OVERVIEW OF MAIN RESULTS

Among the DPS participants with midlife overweight and IGT, long-term glycaemic control and lifestyles were associated with subsequent cognitive performance, while incident diabetes over 13 years was not. Intentional weight loss during the intervention appeared beneficial, but a decrease in weight prior to cognition assessment was related to worse performance.

Among older adults in FINGER, well-targeted dietary counselling was effective and may prevent age-related worsening of diet quality. For global cognition, a long-term healthy diet appears more influential than dietary changes achieved in 2 years. Dietary changes were related to changes in executive functions, indicating that cognitive benefits of dietary modification in older age can be achieved.

### 5.2 INCIDENT DIABETES AND COGNITION (I)

Cognitive performance in the DPS was high and in 2 years CERAD-TS improved, but TMT remained unchanged (Table 5). There was no difference in cognition between the former intervention and control groups, as reported previously (Luchsinger et al. 2015), and thus, all analyses include the groups combined.

Incidence or duration of diabetes had no relationship with cognitive performance in the first assessment, whereas longer duration of diabetes resulted in less improvement in CERAD-TS between the two assessments. This relationship was evident with the categorized variable in the whole population (Table 5) and with the continuous variable in participants with diabetes (CERAD-TS - 0.3 points lower increase for each year with diabetes,  $p=0.042$ ).

Cognitive performance among those <70 years appeared more influenced by exposure to high glycaemia, although their overall performance was higher than in younger participants. There was a significant interaction between the diabetes duration and age (Figure 6), suggesting that diabetes duration was associated with worse CERAD-TS in younger participants, but not among those >70 years (Lehtisalo et al., unpublished results).

**Table 4.** Characteristics of both cohorts.

	DPS		FINGER			
	Participants in the cognition study (n=364)	Non-participants in the cognition study (n=158)	p <sup>1</sup>	Participants in the MITT analyses <sup>2</sup> (n=1155)	Participants not included in the MITT <sup>2</sup> (n=105)	p <sup>1</sup>
Age at baseline	55.1±6.8	55.3±7.8	0.793	69.3±4.7	69.6±4.8	0.520
Age at the 1 <sup>st</sup> cognitive assessment	68.3±6.7					
High education	122 (35%)	50 (32%)	0.686	256 (23%)	26 (25%)	0.521
Women	250 (69%)	100 (63%)	0.265	541 (47%)	47 (45%)	0.683
Intervention group	184 (51%)	81 (51%)	0.924	571 (49%)	60 (57%)	0.131
Diabetes at baseline	0	0		147 (13%)	17 (16%)	0.241
Diabetes after the intervention	70 (19%)	46 (29%)	0.016			
Fasting glucose at baseline	6.1±0.7	6.2±0.8	0.080	6.1±0.9	6.1±0.7	0.682
Systolic BP at baseline	136.8±17.2	140.9±18.4	0.017	140±16	142±16	0.247
CERAD-TS	82.0±9.3			74.7±7.5	73.2±8.3	0.060
TMT-A	48.6±19.6					
NTB total composite score at baseline				0.0±0.6	-0.1±0.7	0.022
DPS goals at baseline <sup>3</sup>	1.0±0.04	1.1±0.08	0.164			
FINGER adherence score at baseline				5.0±1.6	4.7±1.6	0.065

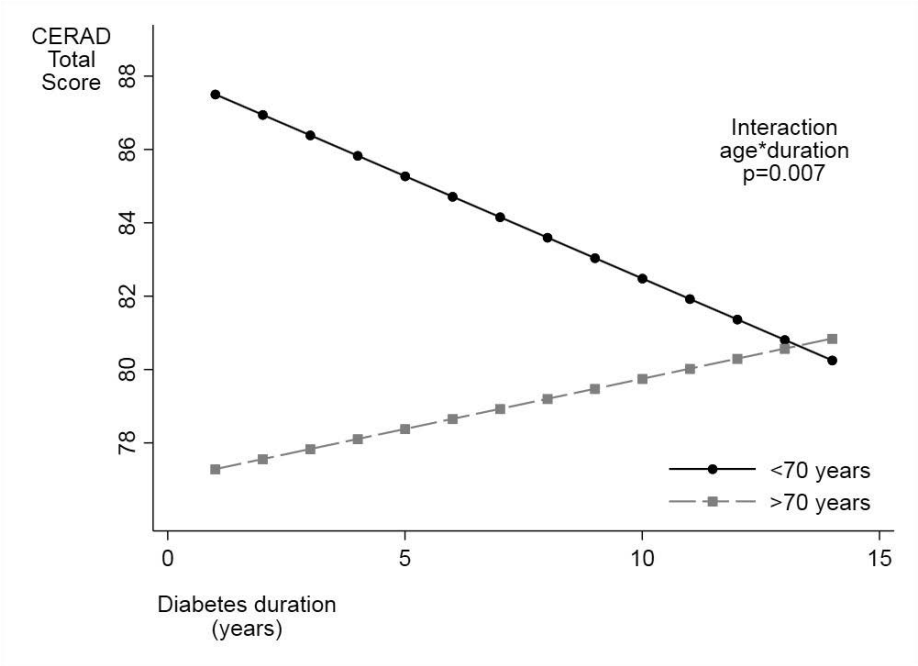
Data are mean±SD or n (%), as appropriate. <sup>1)</sup> p-values for difference between groups from t-test or  $\chi^2$ -test.

<sup>2)</sup> MITT for both cognition and diet, in analysis with only diet, n=1163 <sup>3)</sup> Range 0-4, weight loss goal not possible to evaluate at baseline

**Table 5.** Cognitive performance according to diabetes status at time of cognitive assessment in the DPS cognition study.

		CERAD Total Score			Trail Making Test A		
		mean <sup>1</sup>	(95% CI) <sup>1</sup>	p <sup>2</sup>	mean <sup>1</sup>	(95% CI) <sup>1</sup>	p <sup>2</sup>
<b>First cognitive assessment</b>							
All	(n=364)	82.1	(81.3–82.9)		48.6	(46.7–50.4)	
Without diabetes	(n=193)	82.6	(81.5–83.8)	(ref)	47.4	(44.7–50.0)	(ref)
Verified diabetes	(n=171)	81.5	(80.2–82.7)	0.216	49.9	(47.1–52.7)	0.154
Diabetes <7.5 years	(n=86)	81.7	(80.0–83.4)	0.402	49.5	(45.6–53.4)	0.276
Diabetes >7.5 years	(n=85)	81.2	(79.4–82.9)	0.232	50.3	(46.4–54.3)	0.212
<b>Change between the two assessments</b>							
All	(n=282)	1.0	(0.3–1.7)		0.7	(1.2–2.5)	
Without diabetes	(n=160)	1.3	(0.4–2.2)	(ref)	0.8	(1.6–3.3)	(ref)
Verified diabetes	(n=122)	0.6	(0.5–1.7)	0.144	0.5	(2.4–3.3)	0.661
Diabetes <7.5 years	(n=63)	1.6	(0.1–3.0)	0.860	1.0	(4.9–2.8)	0.222
Diabetes >7.5 years	(n=59)	0.4	(2.0–1.1)	0.023	2.1	(1.9–6.2)	0.564

1) Means and 95% CIs obtained from a linear regression model adjusted for age at the (first) cognitive assessment and educational attainment at baseline. 2) p-values from a model with Box-Cox -transformed cognition scores, and additional adjustment for sex, ApoE4 carrier status, smoking status, systolic blood pressure, and BMI at baseline. Better performance is indicated by higher CERAD-TS and shorter time in the TMT. Improvement in follow-up is indicated by a positive change in the CERAD-TS and a negative change in the TMT.



**Figure 6.** Interaction between diabetes duration and age in cognitive performance measured with the CERAD Total Score. Age categorized at median. Linear regression analysis adjusted for education, sex, ApoE4 carrier status, smoking status, systolic blood pressure, and body mass index at baseline.

### 5.3 LONG-TERM GLYCAEMIA AND COGNITION (I)

Higher HbA1c and 2-hour response to OGTT during the DPS intervention period in midlife were associated with worse performance in the TMT, but not the CERAD-TS (Table 6). These associations were not evident for glycaemia during the post-intervention follow-up closer to the cognitive assessment.

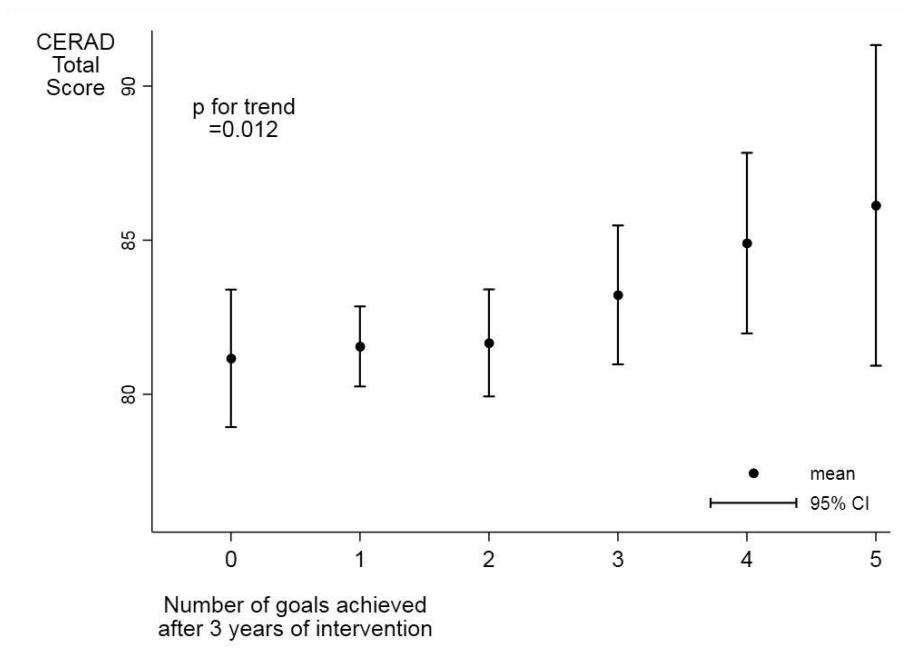
**Table 6.** Cognitive performance according to glycaemia measured during the original intervention period of the DPS in relation to subsequent cognitive performance.

CERAD Total Score					Trail Making Test A		
		<b>b</b>	<b>(95% CI)</b>	<b>p</b>	<b>b</b>	<b>(95% CI)</b>	<b>p</b>
Fasting glucose							
<6.1	(n=176)	(ref)					
6.1–7	(n=143)	0.7	(-1.1–2.5)	0.483	-0.4	(-4.6–3.8)	0.530
>7	(n=45)	-1.5	(-4.2–1.2)	0.433	0.6	(-5.7–6.9)	0.807
	p (trend)			0.759			0.939
2-h glucose							
<7.8	(n=124)	(ref)			(ref)		
7.8–11	(n=197)	-1.3	(-3.1–0.5)	0.105	3.4	(-0.7–7.6)	0.090
>11	(n=43)	-2.1	(-5.0–0.7)	0.232	7.3	(0.9–13.7)	0.018
	p (trend)			0.112			0.012
HbA1c							
<5.7	(n=246)	(ref)			(ref)		
5.76.5	(n=97)	0.0	(-1.8–1.9)	0.947	0.0	(-4.3 –4.3)	0.588
>6.5	(n=20)	-4.1	(-7.8– -0.3)	0.067	11.5	(3.1–19.9)	0.005
	p (trend)			0.210			0.024

Regression coefficients (b) with confidence intervals (95% CIs) represent a difference in cognitive scores compared with the reference group. p-values for trend are obtained from a second model where glycaemia status was entered as a continuous variable. Better performance is indicated by higher CERAD-TS and shorter time in TMT. Regression coefficients are from models using non-transformed cognition scores and p-values from models using Box–Cox -transformed cognition scores adjusted for age at cognitive assessment, education, sex, ApoE4 carrier status, smoking status, systolic blood pressure, and body mass index at baseline.

## 5.4 LONG-TERM LIFESTYLE AND COGNITION (II)

Total amount of achieved lifestyle goals (success score) in the DPS intervention, measured at the third year of the active intervention, predicted better CERAD-TS, but not TMT (Figure 7; TMT not shown). Of the individual lifestyle goals, meeting the total fat intake goal predicted better CERAD-TS ( $p=0.013$ ), but SFA, fibre, weight loss, or PA goals did not. When each of these lifestyle measures was analysed as continuous (mean value over the study period), both lower mean level of total fat and SFA and decreases in these were associated with higher CERAD-TS (Table 7 and Substudy II) and higher level of exercise did too.



**Figure 7.** Total number of DPS intervention goals achieved in the third year of the intervention in relation to subsequent cognitive performance measured with the CERAD Total Score.

The goals include limiting intake of total fat and SFA, increasing intake of fibre, increasing physical activity, and weight loss. Data are presented as mean (95% CI) adjusted for age, education, sex, ApoE4 carrier status, smoking status, systolic blood pressure, and intervention allocation. Point estimates from a model with goal achievement as a categorical variable, and p-value for trend from another model with goal achievement as a continuous variable.



**Table 7.** Linear association between average lifestyle over 13 years and subsequent cognitive performance in the DPS.

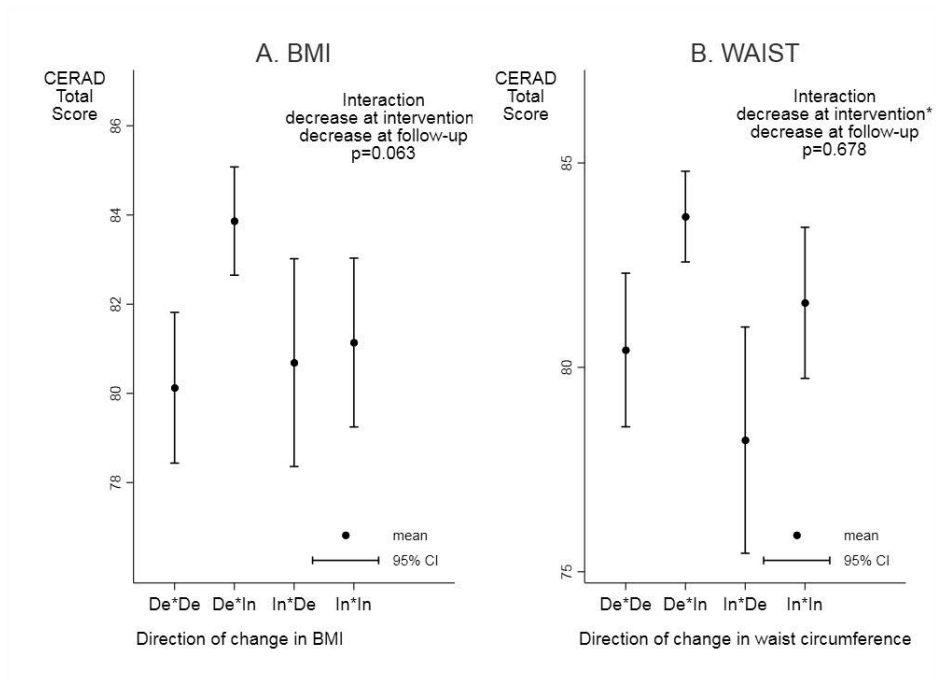
	CERAD Total Score			Trail Making Test A		
	b	(95% CI)	p-value	b	(95% CI)	p-value
Fat intake (E%)	-0.24	(-0.43– -0.04)	0.021	0.31	(-0.14–0.75)	0.228
SFA intake (E%)	-0.41	(-0.73– -0.09)	0.010	0.65	(-0.08–1.38)	0.061
Fibre intake (g/1000 kcal)	0.10	(-0.16–0.36)	0.457	0.11	(-0.49–0.71)	0.627
Moderate-to-vigorous LTPA (h/week)	0.26	(-0.05–0.57)	0.040	-0.19	(-0.91–0.52)	0.538
BMI (kg/m <sup>2</sup> )	-0.23	(-0.41– -0.04)	0.011	0.11	(-0.31–0.53)	0.308
Waist circumference (cm)	-0.09	(-0.16– -0.02)	0.012	0.04	(-0.13–0.21)	0.389

Regression coefficients (b) with confidence intervals (95% CIs) represent change in cognitive scores per one unit increase in lifestyle factors. Regression coefficients are from models using non-transformed cognition scores and p-values from models using Box-Cox - transformed cognition scores. Better performance is indicated by higher CERAD-TS and shorter time in TMT. Model adjusted for age, education, sex, ApoE4 carrier status, smoking status, systolic blood pressure, and BMI at baseline.

## 5.5 WEIGHT LOSS AND COGNITION (II)

Higher BMI or waist circumference during the DPS study period predicted lower CERAD-TS, but changes in these did not (Table 7 and Substudy II). Direction of change in weight was a significant predictor of cognitive performance, but the risk relationship reversed during the post-intervention period. Decrease in BMI during the intervention but increase thereafter resulted in the best CERAD-TS performance, compared with any other group (Substudy II).

When directions of change for both periods (baseline to intervention; intervention to follow-up) were analysed in the same model, decrease in BMI during the intervention period was borderline significant for better CERAD-TS ( $p=0.08$ ), but decrease during the follow-up was significant for worse performance ( $p=0.014$ ), and the interaction between the periods was close to statistical significance ( $p=0.063$ ). For waist circumference, decrease during the intervention predicted better ( $p=0.015$ ) but decrease during the follow-up worse CERAD-TS ( $p=0.004$ ), and there was no indication of an interaction (Figure 8) (Lehtisalo et al., unpublished results).

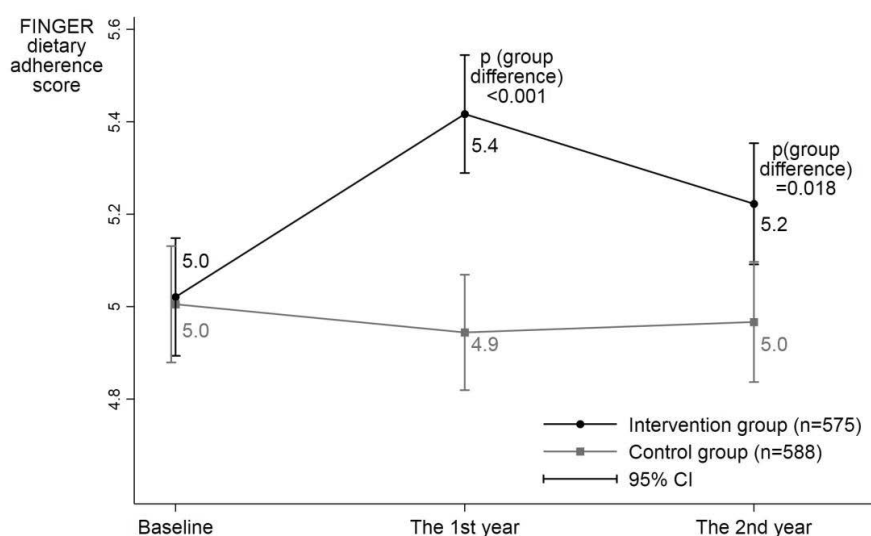


**Figure 8.** Direction of change in BMI (A) and waist circumference (B) in relation to subsequent cognitive performance measured with the CERAD Total Score.

Point estimates for Decrease (at intervention)\*Decrease (at follow-up); Decrease\*Increase; Increase\*Decrease; Increase\*Increase. Data are presented as adjusted mean with error bars indicating 95% CI. Model adjusted for age, education, sex, ApoE4 carrier status, smoking status, systolic blood pressure, and BMI at baseline.

## 5.6 DIETARY INTERVENTION ADHERENCE (III)

The FINGER dietary intervention proved successful, which indicates that among a group of older adults dietary changes are achievable by counselling, even as a part of a multidomain intervention. Diet of the intervention group in the FINGER improved relative to the control group not only in terms of the main goals (Figure 9), but also regarding many other nutrients and food groups (Table 8).



**Figure 9.** Dietary adherence score over two years in the FINGER intervention and control groups.

Point estimates and p-values from a linear mixed model with dietary adherence score as an outcome, group and time as predictors, and time as a random factor. Interaction between group\*time (categorical) represents the difference in change over time.

**Table 8.** Intake and changes in intake of nutrients and foods comprising the FINGER dietary adherence score.

		Intervention group	Control group	Difference <sup>1</sup> between groups		
		mean <sup>2</sup>	mean <sup>2</sup>	mean <sup>2</sup>	SE <sup>2</sup>	p <sup>3</sup>
Saturated and trans FA (E%)	Baseline	13.2	13.0	0.1	0.2	0.431
	Δ 1st year	-0.5	0.7	-1.2	0.2	<0.001
	Δ 2nd year	0.2	1.0	-0.8	0.2	<0.001
Polyunsaturated FA (E%)	Baseline	5.9	6.0	0.0	0.1	0.944
	Δ 1st year	0.8	0.0	0.8	0.1	<0.001
	Δ 2nd year	0.6	0.3	0.4	0.1	0.003
Sucrose (E%)	Baseline	9.0	8.8	0.2	0.2	0.292
	Δ 1st year	-0.4	-0.2	-0.2	0.2	0.194
	Δ 2nd year	-0.6	-0.1	-0.5	0.3	0.051
Fibre (g/d)	Baseline	21.4	22.0	-0.6	0.5	0.229
	Δ 1st year	0.7	-1.2	1.9	0.4	<0.001
	Δ 2nd year	0.1	-1.2	1.3	0.4	0.001
Protein (E%)	Baseline	17.0	16.9	0.2	0.2	0.240
	Δ 1st year	0.0	-0.1	0.1	0.2	0.660
	Δ 2nd year	0.1	-0.1	0.2	0.2	0.371
Alcohol (E%) <sup>4</sup>	Baseline	4.8	5.0	-0.2	0.5	0.537
	Δ 1st year	-0.7	-0.1	-0.6	0.5	0.156
	Δ 2nd year	-0.6	-0.7	0.1	0.5	0.911
Vegetables (g/d)	Baseline	162.8	161.3	1.5	6.1	0.435
	Δ 1st year	12.6	-9.9	22.5	5.5	0.001
	Δ 2nd year	4.9	-6.6	11.5	5.6	0.090
Berries (g/d) <sup>5</sup>	Baseline	55.3	57.7	-2.4	3.7	0.971
	Δ 1st year	9.2	0.1	9.2	4.2	0.060
	Δ 2nd year	4.6	1.7	2.9	4.2	0.658
Fruit (g/d)	Baseline	160.5	158.4	2.1	7.9	0.891
	Δ 1st year	8.7	-6.3	15.1	7.6	0.005
	Δ 2nd year	-5.5	-12.0	6.6	8.0	0.150
Fish and shellfish (g/d) <sup>5</sup>	Baseline	64.3	68.9	-4.6	3.6	0.376
	Δ 1st year	3.4	-7.4	10.8	4.3	0.034
	Δ 2nd year	1.9	-2.6	4.6	4.7	0.353

E%, proportion of total energy intake. SE, standard error.

<sup>1)</sup> Difference in intake at baseline, difference in change at the 1st and the 2nd year.

<sup>2)</sup> Intakes and SE predicted from a mixed model with untransformed intakes as outcome and group and time (categorical) as predictors.

<sup>3)</sup> p-values from models with zero-skewness log transformation for outcomes (modified intention to treat analysis, 575 for intervention and 588 for control).

<sup>4)</sup> Among those using alcohol; 38% of the participants at baseline. Median alcohol intake among all participants at baseline was 0.

<sup>5)</sup> For food groups with <90% consumers at baseline, analyses were carried out among those with some consumption (>0 g). Proportions of consumers (median intake among all participants) at baseline were for berries 83% (23 g) and fish 76% (33 g).

## **5.7 DIETARY SCORE AND COGNITIVE CHANGES WITHIN A MULTIDOMAIN INTERVENTION (IV)**

For examination of diet and dietary changes in relation to cognitive performance and cognitive changes in 2 years, we applied the parallel process growth curve analysis, where latent variables for general level (baseline) and change for both diet and cognition were estimated. Model comparison suggested that the model in which groups were treated as equal (as if there was only one group; Model 6) was the best model for all cognitive outcomes.

Higher dietary adherence score and global cognitive performance at baseline were unrelated, but higher baseline diet score predicted more improvement in global cognition over 2 years (Table 9). Changes in adherence score were not associated with changes in global cognition.

Associations with dietary adherence score varied across cognitive domains. Better baseline diet predicted more change in executive function in the control group (Model 3), but not when the groups were combined (Model 6). Baseline diet predicted also improvements in memory function in combined analyses, and not in the control group alone. In the intervention group, dietary changes were associated with changes in executive function, while this association was only borderline significant in combined analysis. Processing speed showed no associations with cognition in the main analyses.

In an additional model where change in diet was not taken into account (i.e. path between the slopes was constrained to zero), baseline dietary score predicted subsequent cognitive change in all domains (for executive function, path coefficient 0.053;  $p=0.004$ ; and for processing speed, path coefficient= 0.043;  $p= 0.022$ ; intervention and control groups combined).

**Table 9.** Association between total composite cognition score and dietary adherence score during two years estimated with parallel growth curve analysis.

	NTB total composite score			Executive function domain			Memory domain			Processing speed domain		
	path coef.	(SE)	p	path coef.	(SE)	p	path coef.	(SE)	p	path coef.	(SE)	p
Baseline diet → Baseline cognition												
Intervention <sup>1</sup>	0.005	(0.018)	0.780	0.003	(0.022)	0.883	0.017	(0.023)	0.455	0.013	(0.027)	0.640
Control <sup>1</sup>	0.011	(0.018)	0.530	0.008	(0.022)	0.705	0.025	(0.023)	0.279	0.019	(0.027)	0.482
Combined <sup>2</sup>	0.011	(0.018)	0.561	0.003	(0.022)	0.900	0.021	(0.023)	0.346	0.015	(0.027)	0.575
Baseline diet → Cognitive change												
Intervention <sup>1</sup>	0.046	(0.019)	0.014	0.013	(0.031)	0.684	0.075	(0.032)	0.019	0.042	(0.029)	0.141
Control <sup>1</sup>	0.051	(0.019)	0.007	0.041	(0.024)	0.082	0.047	(0.032)	0.140	0.033	(0.026)	0.205
Combined <sup>2</sup>	0.046	(0.016)	0.003	0.028	(0.023)	0.223	0.06	(0.026)	0.022	0.039	(0.022)	0.082
Dietary change → Cognitive change												
Intervention <sup>1</sup>	0.125	(0.094)	0.186	0.390	(0.147)	0.008	0.026	(0.185)	0.890	0.154	(0.158)	0.329
Control <sup>1</sup>	-0.043	(0.113)	0.707	0.200	(0.127)	0.115	-0.136	(0.191)	0.476	-0.016	(0.137)	0.910
Combined <sup>2</sup>	0.052	(0.102)	0.608	0.278	(0.142)	0.051	-0.061	(0.161)	0.702	0.05	(0.125)	0.692

<sup>1</sup>) Model 3 where all model parameters, except from associations between latent variables, are estimated as equal between groups (see Substudy IV for details) <sup>2</sup> Model 6 where all parameters are estimated as equal, as if there was only one group of participants (see Supplement 1 for details). Baseline refers to latent intercept and change refers to latent slope estimated with parallel growth curves. Path coefficient represents one unit change in cognition per one point in dietary score. Models adjusted for age, education (latent variables), study area, sex, and average amount of physical and cognitive activities (observed variables). coef, coefficient; SE, standard error.

## 5.8 INDIVIDUAL DIETARY GOALS AND COGNITIVE CHANGES WITHIN A MULTIDOMAIN INTERVENTION

Additional analyses examined the role of each goal included in the FINGER dietary adherence score (Lehtisalo et al., unpublished results). Only baseline goals were evaluated because changes in individual items were considered unlikely to have a measurable effect on cognitive change based on the results of Substudy IV. Achieving the vegetable goal established a cross-sectional positive association and the alcohol goal a negative association with cognition at baseline (Table 10).

Achieving the fibre goal, vegetable goal, or fruit and berry goal at baseline predicted better subsequent cognitive change, while achieving the alcohol goal predicted worse change. As a continuous variable, higher saturated fat predicted worse cognitive change (b -0.004, p=0.010) and higher intake of polyunsaturated fat better cognitive change (b 0.008, p=0.009), but otherwise linear associations were significant for the same variables that showed associations when categorized as goals.

**Table 10.** Dietary goal achievement at baseline in relation to global cognitive performance measured with the Neuropsychological Test Battery (NTB).

Goal	Criteria	Baseline goal → baseline cognition			Baseline goal → cognitive change		
		b	SE	p	b	SE	p
SFA and trans-FA	<10 E%	-0.039	(0.035)	0.263	0.024	(0.013)	0.068
PUFA	5-10 E%	0.041	(0.030)	0.163	0.014	(0.011)	0.219
Protein	10-20 E%	-0.012	(0.039)	0.753	-0.005	(0.015)	0.751
Sucrose	<10 E%	-0.030	(0.030)	0.307	-0.008	(0.011)	0.482
Fibre	>3 g/MJ	-0.030	(0.029)	0.298	0.039	(0.011)	<0.001
Alcohol	<5 E%	-0.153	(0.042)	<0.001	-0.019	(0.016)	0.239
Vegetable	>200 g/d	0.077	(0.032)	0.015	0.046	(0.012)	<0.001
Fruit and berry	>200 g/d	0.008	(0.029)	0.778	0.028	(0.011)	0.010
Fish and shellfish	any consumption	0.051	(0.030)	0.091	0.025	(0.012)	0.032

E%, proportion of total energy intake. Coefficients (b) with standard error (SE) represent a difference in cognition or cognitive change for those achieving the goal compared with those not achieving the goal. Linear mixed model adjusted for age, education, sex, group, baseline BMI, LDL cholesterol, systolic blood pressure, PA, CA, and total energy intake during the study period.

## **5.9 COMPARISON OF THE POPULATIONS**

For comparison of the populations, descriptive figures for diabetes and CERAD-TS in the FINGER are presented in this section. Self-reported diabetes was prevalent at baseline in 13% (n=164), IGT or IFG in 12% (n=153), and no impairments in glucose metabolism in 75% (n=933) of participants. Five participants with type 1 diabetes (0.5%) were combined with individuals with type 2 diabetes in these comparisons, and data were missing for 10 individuals (1%). Information on duration of diabetes was not collected.

The CERAD-TS in FINGER was on average 75 points among those who were included in the trial, and it improved on average 4 points over 2 years, with no difference in change between the intervention and control groups. Among all participants screened in FINGER (n=2617), the average CERAD-TS was 78 (range 35-98). There was no difference in CERAD-TS at screening in those with and without diabetes, but the group without diabetes improved more in 2 years ( $p=0.041$ ). All participants improved ( $p<0.05$  in paired t-test for each status); those with diabetes on average 2.7 points, those with IGT or IFG 4.8 points, and those without diabetes 4.2 points.

The DPS participants within the age range of the FINGER (60-77 years, n=307) had a mean CERAD-TS of 81 (range 38-99) and a mean change over 2 years of 0.9 points, which was a significant improvement ( $p=0.030$ , paired t-test).



## 6 DISCUSSION

This study investigated the role of lifestyle and lifestyle change within lifestyle interventions at midlife and late life in development of cognitive decline. Results confirm that healthy diet in both midlife and later life predicts better cognitive performance. Moreover, dietary intervention among older adults is effective in promoting dietary change, but evidence of the effectiveness of the dietary intervention for cognitive change is merely suggestive due to the multidomain interventions and the observational nature of the analyses. Nevertheless, findings support promotion of dietary guidelines at both ages to support cognitive functions in older adulthood.

### 6.1 DIABETES PREVENTION AND COGNITIVE PERFORMANCE

#### 6.1.1 DIABETES AND GLYCAEMIA

Contrary to our findings, meta-analyses show relatively consistently that those with diabetes have worse cognitive performance than healthy controls (Monette et al. 2014, Palta et al. 2014, Sadanand et al. 2016). Some studies have reported worse cognition also in IGT patients than in healthy participants (Vanhanen et al. 1998, Lu et al. 2012), but also a difference between IGT and diabetes (Kanaya et al. 2004). Usually, there is no upper limit for diabetes duration in studies with prevalent diabetes, whereas we examined incident diabetes over 13 years. Incident diabetes has predicted more cognitive decline over 5 years (Nooyens et al. 2010), but not over 14 years (Mayeda et al. 2014). A subtle decline in speed has been detected 6 years after the diagnosis of diabetes (Spauwen et al. 2013). All of our participants had baseline IGT and they were likely to have had insulin resistance, which is a risk factor for cognitive decline (Willette et al. 2013, Tortelli et al. 2017), brain atrophy (Tortelli et al. 2017), and amyloid accumulation (Ekblad et al. 2018). This is likely to diminish the effects of diabetes. Also, better control of diabetes has been associated with better cognitive function (West et al. 2014), and presumably, participants in a prevention trial are diagnosed early and treated properly, which may reduce comorbidities.

Participants with a longer duration of diabetes improved less in CERAD-TS over 2 years. Due to the short period between assessments, we hypothesized that this difference would be due to a lack of learning effect, which is often seen with repeated cognitive testing. Diabetes is associated with learning deficits (Ryan, Geckle 2000, McCrimmon et al. 2012), and it has also been

suggested that not all cognitive deficits in diabetes are related to memory impairment, and learning could represent such a deficit.

Cognitive performance among participants <70 years appeared more influenced by exposure to high glycaemia, although their overall performance was higher than that of older participants. Selection could explain this finding, i.e. older adults with longer duration of diabetes no longer participating in the study, but midlife diabetes has been shown to increase the risk for dementia more than diabetes occurring at an older age (Xu et al. 2009, Tolppanen et al. 2013). Those with IGT but no diabetes at the age of >60 years may be less affected by elevated glucose levels and their risk profile may be different. For example, those with earlier onset of diabetes are suggested to have a stronger genetic risk load (Tuomi et al. 2014).

Our results also showed that 2-h glucose and HbA1c levels measured over 9 years predicted subsequent cognition better than diabetes diagnosis, which suggests that the association between glycaemia and cognition exists along a continuum over many years. Also previous studies have reported an association between increasing glucose levels already at “normal” range and increased risk for dementia (Crane et al. 2013, Mortimer et al. 2010) and cognitive deficits (Mortby et al. 2013). Previous literature related to 2-h glucose is limited, but HbA1c has been associated with cognition among those with (Geijselaers et al. 2015) and without diabetes (Ravona-Springer et al. 2012, Marden et al. 2017).

This association was not, however, evident when glycaemia was measured closer to the cognitive assessment period. During this period many participants were already diagnosed with diabetes, and thus, medications may confound the associations, and loss of original intervention targets may diminish the differences between participants. Moreover, the association between elevated glycaemia markers and impaired cognitive performance might not be cumulative, instead having critical periods, and hypothetically, midlife could be such a period. For example, an association between cognitive decline and incident IFG in 2 years has been reported, but not with prevalent stable IFG (Samaras et al. 2014). Among those >70 years, higher fasting glucose has been associated with better cognitive performance (Sims Wright et al. 2015). Long-term glycaemia with multiple measures over many years has not been reported in previous studies.

### **6.1.2 WEIGHT AND WEIGHT LOSS**

Overall, higher BMI and waist circumference predicted worse cognitive performance, but in weight loss the relationship appeared to reverse throughout the study period. Weight loss during the active intervention period comprised a suggestive positive association with subsequent cognition, while weight loss during the follow-up predicted worse performance. It is plausible to assume that weight loss during the intervention was intentional, but after the intervention, confounding by

unintentional weight loss may occur, when weight loss may be consequence of underlying preclinical memory disease. In observational studies, weight loss is present already more than a decade prior to dementia diagnosis (Dahl et al. 2013, Bell et al. 2017). However, among middle-aged participants intentional weight loss appears to establish cognitive benefits (Siervo et al. 2011, Veronese et al. 2017), and some studies suggest the same among over 60-year-olds (Witte et al. 2009, Napoli et al. 2014), but long-term effects (>1 year) have not been evaluated. According to our findings, the distinction between weight loss and weight gain may be more important than the actual amount of weight change, especially closer to the time of cognitive assessment.

### **6.1.3 EXERCISE**

Exercise goal was not associated with cognitive performance in this study, and also the association for continuous moderate-to-vigorous exercise was weak. This is contrary to most of the previous evidence in prospective studies (Sofi et al. 2011). Exercise trials have also shown cognitive benefits among those aged >50 years (Kelly et al. 2014b, Northey et al. 2018), although results regarding the type of exercise were inconsistent. Exercise was a part of the DPS intervention programme, but dietary counselling was more intensive, and thus, dietary changes and weight loss may hinder the possibility to detect effects of exercise in this setting. The lack of associations may also be due to methodological issues, as the exercise goal was measured with a four-category question that is relatively insensitive and does not require very intense exercise compared with trials or observational studies, which usually compare upper and lower extremes. Furthermore, even the more detailed PA variable calculated from a validated questionnaire and used in continuous analyses did not differentiate between the types of exercise. PA in FINGER was not evaluated in this study.

## **6.2 DIETARY INTERVENTION AND COGNITIVE PERFORMANCE**

### **6.2.1 DIETARY INTERVENTION ADHERENCE**

Comprehensive dietary interventions among older adults are scarce, but smaller dietary interventions targeted at participants of retirement age have been shown to be effective in promoting fruit and vegetable intake and also fish intake, while decreasing red meat intake (Lara et al. 2014). Most of these studies have only reported their main goals, one or a few food groups or MeDi defined with a short questionnaire. Our findings on multiple,

simultaneous changes are concordant with a dietary counselling interventions among middle-aged participants that show changes in several micro- and macronutrients (Lindström et al. 2003, Elmer et al. 2006), and also increased compliance to general recommendations (Lin et al. 2007). Among older adults the PREDIMED (Estruch et al. 2013), showed change in fat quality and quantity, but mainly driven by consumption of supplementary olive oil and nuts.

Changes in the adherence score were small, but significantly different between the intervention and control groups. Simultaneous small changes in several nutrients that are not captured in the adherence score may have significance for healthy aging and cognitive performance. Dietary factors that changed into favorable direction were at least partly those that are deficient in a typical Finnish diet, e.g. folate and dietary vitamin D intake, and all of these have been associated with cognitive performance in epidemiological studies. Furthermore, intakes of three nutrients listed as a possible public health concern among community-dwelling older adults (ter Borg et al. 2015), namely vitamin D, riboflavin, and magnesium, were improved during our intervention.

Unfortunately, the improved dietary intakes somewhat attenuated during the second year, when dietary counselling was less active, emphasizing the importance of support for older adults to maintain their dietary changes. Changes in fat quality and whole grain intakes were better sustained also during the second year, as were changes in nutrients to which these food groups contribute to, such as PUFA, fibre and vitamin E. Also a previous study has suggested that changes in fat intake were easier to maintain than those in fruit and vegetable intake (Lapointe et al. 2010), and fat and fibre intake changes were also well sustained in the DPS (Lindstrom et al. 2013).

### **6.2.2 INDIVIDUAL DIETARY GOALS**

Most previous studies investigating diet and cognition have single dietary assessment, after which cognitive change is measured over many years. Convergent with our findings in both populations, higher saturated fat intake has been associated with cognitive decline over 4 to 6 years (Morris et al. 2004, Okereke et al. 2012), also among those with diabetes (Devore et al. 2009), while contradictory observations exist as well (Vercambre et al. 2010, Naqvi et al. 2011). Two studies showed benefit of higher intake of MUFA (Naqvi et al. 2011, Okereke et al. 2012). Not adjusting for other dietary fats could produce inconclusive results (Morris, Tangney 2014), since fatty acids yielded from same sources have protective and harmful effects on cognition, and they are highly correlated, such as MUFA and SAFA. Total fat is typically not analysed in observational studies, as the interest lies in the quality of fat, and no previous data exists. In the DPS decrease in total fat was due to decrease in SFA (Lindström et al. 2003) and thus mainly reflects that.

In both the DPS and the FINGER, no difference was observed between those reaching and not reaching the SFA goal (<10 E%) though, which could suggest that the cut-off was suboptimal, as an effect was seen when using continuous SFA measure. More plausible explanation would be the small number of participants reaching the goal, which may hinder the possibility to detect statistically significant difference. Also, any decrease in the proportion of energy from SFA may be beneficial, even above the 10E%. Similarly, the PUFA goal in the FINGER was insignificant but continuous intake established linear association with cognitive performance. This goal was on the other extreme with most of the participants reaching the goal. Anyhow, associations between dietary factors and cognitive factors are likely to be continuous, although not necessarily linear, and establishing cut-offs is always somewhat arbitrary.

The few existing studies of dietary fibre and cognition suggest positive association (Ortega et al. 1997, Vercambre et al. 2009), as well as for whole grain (Wengreen et al. 2013) and non-refined cereal (Anastasiou et al. 2017). We did not find such association in the DPS, only in FINGER. In the DPS, larger changes implemented in dietary fat intake, in both intervention and control, could have exceeded the importance of fibre. Alternatively, benefits of fiber may be more immediate as all previous studies have had shorter follow-up than did the DPS.

Because the FINGER adherence score was grounded on general recommendations, it may have included components that irrelevant for brain health, and would thus decrease the sensitivity of the score. Based on additional analyses, protein and sucrose intakes appear such components. Also the fish goal shows insignificant associations, but this result should be interpreted with caution since our method is suboptimal for estimating fish intake. There is evidence showing benefits of fish consumption (Samieri et al. 2018), especially among older adults (Qin et al. 2014). Otherwise, these findings are in accordance with previous beneficial effects reported for vegetables and fruits (Chen et al. 2012) and the above-mentioned fats and fibre, although for all of these dietary factors the evidence is more convincing in relation to the risk for dementia than for cognition among non-demented participants.

Alcohol intake has shown a positive association with cognitive function also in previous studies (Almeida et al. 2014, Kim et al. 2016, Reas et al. 2016), one of which found an association only with red wine and speculated the effects to be due to non-alcoholic components of the wine (Nooyens et al. 2014). Based on our goal analysis, those with higher than moderate alcohol consumption showed better cognitive performance than moderate consumers, but healthy user bias and uncertainties related to reliability of reporting of alcohol intake should be taken into account when interpreting these observational findings, especially since this association was only evident cross-sectionally at baseline. This approach also did not differentiate

never-consumers from former consumers, which could be important (Ilomaki et al. 2015, Hassing 2018).

### **6.2.3 DIETARY SCORE**

No observational studies have analysed the association between dietary changes in relation to cognitive changes, and few dietary intervention trials have tested the effect of dietary modification. In comparison with our findings, the PREDIMED substudy that assessed cognitive change over 5 years reported a benefit in frontal cognition, including attention and executive function, for the MeDi+olive oil group, and in memory for the MeDi+nuts group (Valls-Pedret et al. 2015). We also showed an association between dietary adherence score changes and change in executive function, whereas for the memory domain only baseline diet appeared influential. Possibly, benefits for the memory domain may take longer to manifest, as our trial lasted for 2 years as compared with 5 years in the PREDIMED.

It remains to be evaluated whether executive functions are the only cognitive domain responsive to dietary modification in older age, whether dietary adherence to national guidelines is more beneficial for executive domain, or whether a longer exposure is needed for other domains. Executive and attention impairment may be among the earliest signs of underlying preclinical AD (Mortamais et al. 2017), and hence, could be the first domain to show an effect for lifestyle modification. Executive functions have also been traditionally related to vascular type of cognitive impairment (Sudo et al. 2017), and given that the adherence score is based on national dietary recommendations mainly based on evidence linking diet to cardiovascular health, the effect of dietary changes for changes in executive function could be mediated through vascular factors.

Similar results for a healthy baseline diet predicting better cognitive change over time have been reported for the MeDi (Tangney et al. 2011, Galbete et al. 2015, Qin et al. 2015), the MIND (Morris et al. 2015a) and the DASH (Wengreen et al. 2013) in populations aged >65 years. Many of these studies also report a cross-sectional association at baseline, which was not evident in our study. Selection of participants may explain the lack of such an association; those with the highest and lowest cognitive performance at baseline were excluded from the study, and thus, associations at baseline may be more difficult to observe.

Dietary changes during an intervention have been shown to be associated with a simultaneous change in telomere length (Garcia-Calzon et al. 2015), and a similar parallel growth curve analysis has been exploited to show the effect of dietary and exercise changes in weight changes in a longitudinal setting without an intervention (Kim et al. 2017). The relationship of dietary modification versus long-term healthy diet in relation to several health outcomes in older age should be studied in more detail.

## 6.3 CRITICAL EVALUATION OF THE STUDY

### 6.3.1 SETTINGS

Strengths of the DPS include reliable diagnosis of diabetes and extensive data of repeated assessments for glycaemia, diet, exercise, and weight over many years prior to cognitive assessment. Most of the previous studies rely on a single measure of predictors, even if the cognitive outcomes were measured more frequently. The average of lifestyle measures over a long period is likely to produce a more reliable estimate of long-term status. Especially for weight, these frequent assessments appear important since we were able to separate patterns of weight loss during distinct periods. The diabetes criteria used were from 1985 (World Health Organization 1985), and more participants would have been diagnosed with the current criteria (World Health Organization 1999).

The main limitation of the DPS was the ancillary cognitive assessment, which was carried out almost 10 years after the intervention. Lack of baseline cognition data makes the interpretation of the cognitive results more difficult; it is not possible to separate those undergoing a decline from those with a low general cognitive performance, and those who achieved and maintained a healthier lifestyle during the study may have had better cognitive performance at the outset. In any case, participants were relatively young and had a high cognitive performance even at the end of our follow-up.

Strengths in the FINGER include a large population-based sample, detailed data for both cognition and diet, good adherence to the intervention, and a low drop-out rate. Concerning the prespecified secondary analysis of intervention effect on diet, the main limitations are related to dietary methodology, which will be discussed in the next section. Regarding the associations between diet and cognition, the main limitation is the multidomain nature of the intervention, which can never be fully accounted for in analyses focusing on a single exposure of interest, and speculation about the role of other lifestyle changes remains. However, we adjusted our analyses for average level of PA and CA, without any notable modification of the results. Also, the presented associations between 2-year changes in both diet and cognition were fairly similar in both intervention and control groups. Even in RCTs, analyses that are not investigating directly the difference between intervention and control groups are prone to clustering of healthy lifestyle factors, similar to observational studies, i.e. participants with a healthier diet are more likely to also have otherwise healthy lifestyles.

The analysis of an association between two time-dependent variables and changes in them is complicated. We applied a sophisticated statistical method, namely the parallel growth curves, which is suggested to be the most suitable for analysing change when at least three measures are available, especially when associations between changes in two variables are of interest

(Singer, Willet 2003, Curran et al. 2010). Still, this analysis is exploratory, and 2 years with only three assessments is a limitation when estimating change. Lack of statistical power may restrict the possibilities to detect associations, and some associations might require a latency period, and thereby, analysis of simultaneous changes would not be optimal.

In both of our studies, as in any longitudinal study, long-term participation in the study may have resulted in selection of more health-conscious participants, and it may also have impacted the health behaviours in the control groups, diminishing the differences between groups. Study visits provide information about health, and regular feedback is likely to modify behaviour. In both studies, selection of cognitively healthier participants is a likely source of bias. Those with cognitive problems are typically not able or willing to participate and are lost during a long follow-up.

Despite midlife overweight and IGT, the DPS participants had high global cognitive performance, and also in an age-matched sub-population cognitive performance was better than in the FINGER. This is expected because the FINGER participants were selected based on elevated cognitive risk, and persons with high performance in the CERAD were excluded at the screening visit. Improvement in 2 years was greater in the FINGER when measured with the CERAD-TS, also in the control group. Probably, predisposition to an extensive cognitive testing annually in the FINGER resulted in more learning than in the CERAD within a 2-year interval, and there also was more room for improvement in the FINGER. However, in both populations having diabetes resulted in less improvement in 2 years than in participants with no diabetes.

### **6.3.2 DIETARY ASSESSMENT**

Both studies collected 3-day food records to estimate dietary intake. For group comparisons presented in Substudy III, this method is well suited, while reliable estimation of usual intake at the individual level would require a longer period for most nutrients, and preferably non-consecutive days. Using a 3-day food record to assess diet is thus likely to cause more error variation, especially when analysing change over time, due to high within-subject variation between the assessments. However, these issues are likely to add random error and decrease statistical power, and hence, type II error (“false negative”), but are not susceptible to causing type I error (“false positive”). Furthermore, the long-term diet in the DPS was defined based on several records, and in the FINGER statistical methods chosen are supposed to decrease error variation when individual trajectories are estimated with structural equation modelling.

Participation in the intervention may also affect participants’ reports of their diet, and use of a self-reported diet as an outcome of studies has been criticized (Keogh et al. 2016). Intervention groups may overreport their



intake of healthy foods or be more interested in recording well. However, there are no biomarkers for most nutrients of interest and no methods for measuring dietary patterns objectively. In the DPS, real dietary changes are plausible, as a significant treatment effect was observed. Between-group comparisons in the FINGER (III) may be prone to recording differences, but a decline in dietary quality in the intervention during the second year can be viewed as a sign of actual changes since improvements in recording would, hypothetically, have been maintained throughout the study period.

Errors in reporting diet with FFQ have been described with cognitive problems (Pope et al. 2007, McNeill et al. 2009), but it is not known whether these errors also occur with food records, or whether persons with cognitive performance at an average or slightly lower level would make more reporting errors than other older adults. Recording is recommended immediately after eating and does not require remembering, but tasks like estimating portion sizes could be demanding with cognitive problems. In the DPS, where diet was measured several years prior to cognitive assessments, any bias related to low cognitive abilities is less likely.

The FINGER dietary adherence score is based on national recommendations, which makes it clinically relevant but also rather insensitive since scoring of its components is dichotomous. Dietary recommendations were updated during our study period, but changes in the included items were minor, mostly wider ranges for macronutrient intakes. Since we planned and executed our intervention, the first dietary index developed specifically to support brain health, namely the MIND, has been introduced, and evidence related to MeDi and DASH has accumulated. Retrospectively observed, the FINGER intervention has included most of the MIND components (i.e. adding whole grains, vegetables and berries, fish, and poultry, and limiting alcohol, butter, and sweet pastries), with some national modifications (rapeseed vs. olive oil), and evidently the main characteristics of all of these dietary indices are similar.

Superiority of the dietary patterns remains unclear, and they have been shown to yield similar results in the same populations, both related to cognition (Wengreen et al. 2013) and other outcomes (Liese et al. 2015, Drake et al. 2011). No new evidence has emerged in recent years that would have made the recommended dietary intervention targets in FINGER outdated. Also the additional results in this summary suggest that most of the components appear relevant, while the sensitivity of the score could be improved with alternative scoring. The choice of an alternative method should be carefully considered. Tertiles or quartiles of consumption are widely used, but it has been argued that scoring based on absolute consumption should be preferred over relative scoring (distribution of the sample) (Morris 2016). For MeDi and DASH, both scoring methods have been used. Predefined cut-offs could be more suitable for men, but sample-based for women (Drake et al. 2013).

### **6.3.3 COGNITION ASSESSMENT**

Two sets of neuropsychological tests were used. The study nurse conducted the simple CERAD in the DPS, while the study psychologist conducted the NTB in the FINGER, a set of validated and widely used tests that have previously been shown to be sensitive to early AD. The total scoring method for the CERAD gives a more sensitive measure of global cognition than any subtests, and it has been shown to distinguish well between MCI or prodromal AD and healthy controls (Paajanen et al. 2010, Paajanen et al. 2014). However, studies among non-demented populations are lacking, and hence, the sensitivity of this score to detect changes in this population is uncertain. Hypothetically, with more sensitive tests more differences could have emerged.

Improvement in both groups in the FINGER went against the original assumption, and it may have diminished the possibilities to detect associations between cognition and lifestyle. The FINGER intervention group also had a lower proportion of those who actually declined in 2 years, but these data were not analysed in this study. The relevance of these cognitive changes in relation to AD remains unclear until the longer follow-up of the FINGER is completed.

The general improvement detected in both populations also highlights the importance of a control group. Many smaller scale lifestyle intervention trials are executed without a control group, or they compare two sets of intervention and conclude, perhaps erroneously, the benefit of both. The FINGER control group received a mini-intervention and participated actively, which may have served as an additional intervention. However, it is clear that not all improvement in the tests of non-demented adults is attributable to the intervention effect, but also learning effects occur due to repeated cognitive testing.

## **6.4 RESULTS IN THE CONTEXT OF LIFESTYLE AND PREVENTION OF COGNITIVE DECLINE**

Despite the observational nature of the cognition analyses, the reasoning for this study lies in estimating the possibilities to prevent cognitive decline with lifestyle interventions. Two separate approaches to study prevention of cognitive decline were applied, namely prevention through intervening risk factors (diabetes) in midlife and prevention through lifestyle intervention in older age. Many of the targeted lifestyles were similar.

Currently, no clear evidence supports the prevention of cognitive decline through interventions that postpone or treat diabetes. Previously published results showed no difference in cognitive performance between the original intervention and control groups of the DPS (Luchsinger et al. 2015). It was speculated that the follow-up time may have been too short to manifest effects, as the participants were still relatively young, or the lack of statistical

power or cohort attrition may have hindered the detection of differences. While all of these considerations are still relevant, since that publication a very similar diabetes prevention study in the US also found no effect on cognition (Luchsinger et al. 2017), as did trials reporting cognitive performance after various treatments for diabetes (Koekkoek et al. 2012, Murray et al. 2017, Rapp et al. 2017). All of the forementioned added cognition as an ancillary measure after the intervention and may thus suffer from insufficient statistical power, dilution of treatment goals, and lack of baseline assessment. Trials that measured cognitive change during the intervention suggested improvement after 6 months of exercise among those with IGT (Baker et al. 2010) and improved diabetes control among older participants with diabetes (Luchsinger et al. 2011). Also our results suggest that controlling glycaemia levels with lifestyle is beneficial in IGT. However, the possibility that diabetes and dementia do not have a causal association but similar underlying factors that result in co-occurrence of these diseases must also be considered. In that case, interventions among those with diabetes or even those with risk for diabetes could be an insufficient strategy.

Evidence related to diet in prevention of cognitive decline is heterogeneous and scattered. Clinical trials were initiated with dietary supplements, most of which have failed over the years. This may partly be attributable to the same reasons suggested for failure in most pharmacological trials, e.g. unselected populations, too short follow-up, and intervening too late. The phenomenon of observational studies constantly showing a benefit of supplements that are subsequently proven not to be effective is hardly unique and has been demonstrated with, for instance, vitamins in relation to CVD or cancer (Fortmann et al. 2013). Dietary intake of one nutrient always has an impact on the intakes of several others, and changes in them are correlated. Moreover, effects may require a correct combination of nutrients provided by the diet rather than by a single nutrient in a supplement. In general, supplementations appear unnecessary if no deficiency of nutrients is evident. At the same time, presence of subclinical deficiency or at least dietary intake below the recommended level is common among older adults, and benefits are more likely if these participants are targeted.

Trials with dietary modification rather than supplementation retain more potential, but they are demanding in terms of adherence and costs. Despite their disease prevention potential, dietary changes are more likely to be effective if occurring in midlife or earlier and maintained thereafter, which is difficult to demonstrate in an RCT setting. There is a possibility that a long-term diet is too influential to allow any measurable effect of changes after a certain period, e.g. midlife. Still, our results in Substudy IV, together with the PREDIMED (Valls-Pedret et al. 2015), support the idea of beneficial dietary changes in older age in relation to cognitive changes, even though the baseline diet appeared more influential over 2 years. This complex association between long-term diet and dietary changes in different phases of

life should be elucidated. Better understanding of the transition from midlife, where dietary prevention trials have mostly focused on CVD risk factors, to older age, where trials have usually focused on frailty and maintenance of functional abilities, would be important also in terms of promoting cognitive performance. In the diet context, the relative importance of CVD-related factors like salt and fat quality, securing adequate dietary intake, and preventing deficiencies is likely to be different in different phases of life, but optimal dietary approaches and identification of these phases remain to be identified. However, our results support the idea that similar dietary interventions are suitable and provide cognitive benefits in midlife and older age, with only slight modifications and tailoring required over the lifespan.

Currently, the evidence for possibilities to prevent cognitive decline with diet is promising but scattered. While this study adds detailed and extensive information to the existing data, more studies on the relationship between dietary factors and cognition are needed.

## 7 CONCLUSIONS AND FUTURE PERSPECTIVES

Healthy lifestyles targeted in interventions during midlife and later life are associated with better late-life cognitive performance. The main findings here can be summarized as follows:

- I. Among a group with IGT, incident diabetes over 13 years was unrelated to cognitive performance, but maintaining glucose metabolism at a normal level in midlife predicted better visuomotor speed later in life. Age modified these associations, and the effect of hyperglycaemia on cognition was stronger among younger participants.
- II. Meeting the DPS intervention goals in midlife predicted better global cognitive performance later in life, and long-term dietary fat intake, especially saturated fat, weight, and waist circumference showed linear inverse associations with subsequent global cognitive performance. Decreases in weight and waist circumference during the original lifestyle intervention demonstrated a positive association and decreases prior to cognition assessment a negative association with global cognition. Weight loss in late life might be unintentional and a marker of an ongoing disease process.
- III. Dietary intervention among older adults was feasible as part of an intensive multidomain intervention. The intervention group adopted simultaneous favourable changes in several energy-yielding nutrients, vitamins, and foods, and overall diet quality improved compared with the control group.
- IV. Better dietary quality at baseline measured with the FINGER adherence score predicted more improvement over 2 years in global cognition and in all studied cognitive domains, namely executive function, processing speed, and memory. Dietary changes achieved during the intervention were positively associated with changes in executive function, suggesting a benefit of dietary counselling.

The main implications for clinical practice and future research can be summarized as follows:

1. General dietary recommendations appear suitable for the prevention of cognitive decline, especially better quality of fat and carbohydrate, already in midlife and also in older age.
2. Individually tailored dietary counselling is effective among older adults, but maintenance of adopted dietary changes requires support.
3. The effect of weight loss appears to shift from beneficial to detrimental between midlife and older age, and future studies should distinguish between voluntary and involuntary weight loss.
4. Late-life weight loss should be studied as a target for prevention if prevention of weight loss is shown to help in maintaining cognitive abilities.
5. Age of onset of diabetes and metabolic disturbances should be better understood in relation to later cognitive performance. Future studies should collect precise data on age at diabetes diagnosis and duration of diabetes to clarify the previously inconsistent findings among non-demented older adults and to help in targeting interventions.
6. Identification of dietary and other lifestyle approaches influential in older age, as compared with approaches utilized already in midlife, is important to support healthy cognitive ageing and also healthy ageing overall.

## ACKNOWLEDGEMENTS

Numerous people have contributed in one way or another to this thesis; I am indebted to them all. This study was carried out at the National Institute for Health and Welfare (THL) and I thank all heads of the Departments and Units for whom I have worked for providing excellent facilities and for the freedom to do my own research. Special thanks go to Research Professor Markku Peltonen, a long-time Head of our Unit, for always being supportive.

I am most grateful for funding received for this study – my gratitude goes to the Juho Vainio Foundation, the Yrjö Jahnsson Foundation, and the Finnish Cultural Foundation for believing in this study already at its inception, and to the Doctoral Programme in Population Health at the Faculty of Medicine, University of Helsinki, for providing funding for the last two years. I am especially grateful to Professor Ossi Rahkonen for helping and supporting me over the years.

I sincerely thank the official reviewers of this thesis, Professor Anne Remes and Adjunct Professor Jaana Laitinen, for constructive comments and new perspectives, and author-editor Carol Ann Pelli for careful language revision and valuable comments. I also wish to thank Associate Professor Nikolaos Scarmeas for accepting the role of opponent at the defence.

My deepest gratitude goes to my supervisors, Professor Miia Kivipelto and Adjunct Professors Jaana Lindström and Tiia Ngandu. You all had a crucial role in my journey; none of this work would have been possible without Miia, I would not have started my own project without Jaana, and I would never have completed it without Tiia. Thank you for sharing professional insights and for believing in me and always encouraging me.

I have been privileged to work with amazing people, and it is not possible to list everyone who has had an impact on my rather long PhD journey. To name but a few, Esko Levälahti provided me with invaluable statistical advice, and Teemu Paajanen and Tuomo Hänninen helped in understanding neurocognitive data. I also wish to thank Satu Ahtiluoto for her contribution to the coordination of FINGER, and Päivi Valve for help in setting up the dietary intervention. Jenni Kulmala, Francesca Mangialasche, and Alina Solomon, although you had no official role in this thesis, you have been sources of both expertise and inspiration for me.

I am grateful to the study group of the DPS for allowing me to use their data; the steering group of the FINGER for taking me in as a junior member and teaching me so much about doing research; all of my co-workers at the institute who have shared lunches and coffee breaks and many ups and downs over the years; and research personnel in both studies for making data collection possible. Special thanks go to the nutritionists in the FINGER trial for excellent guidance and to everyone who participated in dietary data collection. I am also greatly indebted all my co-authors for sharing their

expertise and providing valuable criticism and comments. And the last but not least, I sincerely thank the participants and their close relatives for their time and effort in making this project a reality.

On a personal note, I deeply thank my family and all of my friends outside the research world. My parents have always supported and loved me and have given a tremendous amount of help with the practicalities of everyday life. My dear friends have the ability to cheer me even on the dreariest of days. But above all, the biggest source of inspiration and strength is my own family, and every day I am grateful to Jaakko and our beloved son Aarni, thank you both for being there for me.

Helsinki, October 2018

Jenni Lehtisalo



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